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(54) Title: EXTENDED cDNAs FOR SECRETED PROTEINS

#### (57) Abstract

The sequences of extended cDNAs encoding secreted proteins are disclosed. The extended cDNAs can be used to express secreted proteins or portions thereof or to obtain antibodies capable of specifically binding to the secreted proteins. The extended cDNAs may also be used in diagnostic, forensic, gene therapy, and chromosome mapping procedures. The extended cDNAs may also be used to design expression vectors and secretion vectors.

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#### EXTENDED cDNAS for secreted proteins

The present application relates to extended cDNAs which were disclosed in several United States Provisional Patent Applications. Table I lists the SEQ ID Nos. of the extended cDNAs in the present application, the SEQ ID Nos. of the identical or nearly identical extended cDNAs in the provisional applications, and the identities of the provisional applications in which the extended cDNAs were disclosed.

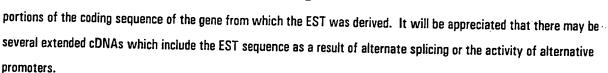
#### Background of the Invention

The estimated 50,000·100,000 genes scattered along the human chromosomes offer tremendous promise for the understanding, diagnosis, and treatment of human diseases. In addition, probes capable of specifically hybridizing to loci distributed throughout the human genome find applications in the construction of high resolution chromosome maps and in the identification of individuals.

In the past, the characterization of even a single human gene was a painstaking process, requiring years of effort. Recent developments in the areas of cloning vectors, DNA sequencing, and computer technology have merged to greatly accelerate the rate at which human genes can be isolated, sequenced, mapped, and characterized. Cloning vectors such as yeast artificial chromosomes (YACs) and bacterial artificial chromosomes (BACs) are able to accept DNA inserts ranging from 300 to 1000 kilobases (kb) or 100-400 kb in length respectively, thereby facilitating the manipulation and ordering of DNA sequences distributed over great distances on the human chromosomes. Automated DNA sequencing machines permit the rapid sequencing of human genes. Bioinformatics software enables the comparison of nucleic acid and protein sequences, thereby assisting in the characterization of human gene products.

Currently, two different approaches are being pursued for identifying and characterizing the genes distributed along the human genome. In one approach, large fragments of genomic DNA are isolated, cloned, and sequenced. Potential open reading frames in these genomic sequences are identified using bio-informatics software. However, this approach entails sequencing large stretches of human DNA which do not encode proteins in order to find the protein encoding sequences scattered throughout the genome. In addition to requiring extensive sequencing, the bio-informatics software may mischaracterize the genomic sequences obtained. Thus, the software may produce-false positives in which non-coding DNA is mischaracterized as coding DNA or false negatives in which coding DNA is mischaeled as non-coding DNA.

An alternative approach takes a more direct route to identifying and characterizing human genes. In this approach, complementary DNAs (cDNAs) are synthesized from isolated messenger RNAs (mRNAs) which encode human proteins. Using this approach, sequencing is only performed on DNA which is derived from protein coding portions of the genome. Often, only short stretches of the cDNAs are sequenced to obtain sequences called expressed sequence tags (ESTs). The ESTs may then be used to isolate or purify extended cDNAs which include sequences adjacent to the EST sequences. The extended cDNAs may contain all of the sequence of the EST which was used to obtain them or only a portion of the sequence of the EST which was used to obtain them. In addition, the extended cDNAs may contain the full coding sequence of the gene from which the EST was derived or, alternatively, the extended cDNAs may include



In the past, the short EST sequences which could be used to isolate or purify extended cDNAs were often 5 obtained from oligo-dT primed cDNA libraries. Accordingly, they mainly corresponded to the 3' untranslated region of the mRNA. In part, the prevalence of EST sequences derived from the 3' end of the mRNA is a result of the fact that typical techniques for obtaining cDNAs, are not well suited for isolating cDNA sequences derived from the 5' ends of mRNAs. (Adams et al., Nature 377:174, 1996, Hillier et al., Genome Res. 6:807-828, 1996).

In addition, in those reported instances where longer cDNA sequences have been obtained, the reported sequences typically correspond to coding sequences and do not include the full 5' untranslated region of the mRNA from which the cDNA is derived. Such incomplete sequences may not include the first exon of the mRNA, particularly in situations where the first exon is short. Furthermore, they may not include some exons, often short ones, which are located upstream of splicing sites. Thus, there is a need to obtain sequences derived from the 5' ends of mRNAs which can be used to obtain extended cDNAs which may include the 5' sequences contained in the 5' ESTs.

While many sequences derived from human chromosomes have practical applications, approaches based on the identification and characterization of those chromosomal sequences which encode a protein product are particularly relevant to diagnostic and therapeutic uses. Of the 50,000-100,000 protein coding genes, those genes encoding proteins which are secreted from the cell in which they are synthesized, as well as the secreted proteins themselves, are particularly valuable as potential therapeutic agents. Such proteins are often involved in cell to cell communication and 20 may be responsible for producing a clinically relevant response in their target cells.

In fact, several secretory proteins, including tissue plasminogen activator, G-CSF, GM-CSF, erythropoietin, human growth hormone, insulin, interferon- $\alpha$ , interferon- $\beta$ , interferon- $\gamma$ , and interleukin-2, are currently in clinical use. These proteins are used to treat a wide range of conditions, including acute myocardial infarction, acute ischemic stroke, anemia, diabetes, growth hormone deficiency, hepatitis, kidney carcinoma, chemotherapy induced neutropenia and 25 multiple sclerosis. For these reasons, extended cDNAs encoding secreted proteins or portions thereof represent a particularly valuable source of therapeutic agents. Thus, there is a need for the identification and characterization of secreted proteins and the nucleic acids encoding them.

In addition to being therapeutically useful themselves, secretory proteins include short peptides, called signal peptides, at their amino termini which direct their secretion. These signal peptides are encoded by the signal sequences 30 located at the 5' ends of the coding sequences of genes encoding secreted proteins. Because these signal peptides will direct the extracellular secretion of any protein to which they are operably linked, the signal sequences may be exploited to direct the efficient secretion of any protein by operably linking the signal sequences to a gene encoding the protein for which secretion is desired. This may prove beneficial in gene therapy strategies in which it is desired to deliver a particular gene product to cells other than the cell in which it is produced. Signal sequences encoding signal peptides

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also find application in simplifying protein purification techniques. In such applications, the extracellular secretion of the desired protein greatly facilitates purification by reducing the number of undesired proteins from which the desired protein must be selected. Thus, there exists a need to identify and characterize the 5' portions of the genes for secretory proteins which encode signal peptides.

Public information on the number of human genes for which the promoters and upstream regulatory regions have been identified and characterized is quite limited. In part, this may be due to the difficulty of isolating such regulatory sequences. Upstream regulatory sequences such as transcription factor binding sites are typically too short to be utilized as probes for isolating promoters from human genomic libraries. Recently, some approaches have been developed to isolate human promoters. One of them consists of making a CpG island library (Cross, S.H. et al., 10 Purification of CpG Islands using a Methylated DNA Binding Column, Nature Genetics 6: 236-244 (1994)). The second consists of isolating human genomic DNA sequences containing Spel binding sites by the use of Spel binding protein. (Mortlock et al., Genome Res. 6:327-335, 1996). Both of these approaches have their limits due to a lack of specificity or of comprehensiveness.

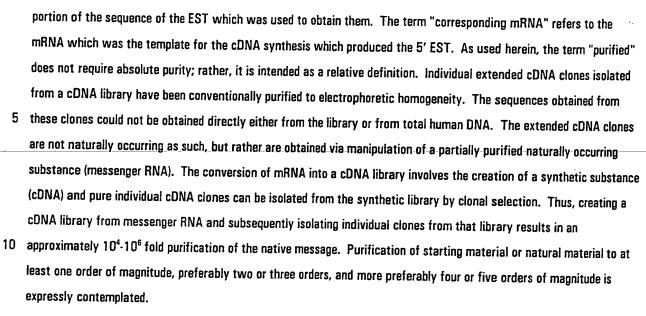
5' ESTs and extended cDNAs obtainable therefrom may be used to efficiently identify and isolate upstream 15 regulatory regions which control the location, developmental stage, rate, and quantity of protein synthesis, as well as the stability of the mRNA. (Theil et al., BioFactors 4:87-93, (1993). Once identified and characterized, these regulatory regions may be utilized in gene therapy or protein purification schemes to obtain the desired amount and locations of protein synthesis or to inhibit, reduce, or prevent the synthesis of undesirable gene products.

In addition, ESTs containing the 5' ends of secretory protein genes or extended cDNAs which include sequences adjacent to the sequences of the ESTs may include sequences useful as probes for chromosome mapping and the identification of individuals. Thus, there is a need to identify and characterize the sequences upstream of the  $5^{\prime}$ coding sequences of genes encoding secretory proteins.

### Summary of the Invention

The present invention relates to purified, isolated, or recombinant extended cDNAs which encode secreted 25 proteins or fragments thereof. Preferably, the purified, isolated or recombinant cDNAs contain the entire open reading frame of their corresponding mRNAs, including a start codon and a stop codon. For example, the extended cDNAs may include nucleic acids encoding the signal peptide as well as the mature protein. Alternatively, the extended cDNAs may contain a fragment of the open reading frame. In some embodiments, the fragment may encode only the sequence of the mature protein. Alternatively, the fragment may encode only a portion of the mature protein. A further aspect of the present invention is a nucleic acid which encodes the signal peptide of a secreted protein.

The present extended cDNAs were obtained using ESTs which include sequences derived from the authentic 5' ends of their corresponding mRNAs. As used herein the terms "EST" or "5' EST" refer to the short cDNAs which were used to obtain the extended cDNAs of the present invention. As used herein, the term "extended cDNA" refers to the cDNAs which include sequences adjacent to the 5' EST used to obtain them. The extended cDNAs may contain all or a



As used herein, the term "isolated" requires that the material be removed from its original environment (e.g., the natural environment if it is naturally occurring). For example, a naturally-occurring polynucleotide present in a living animal is not isolated, but the same polynucleotide, separated from some or all of the coexisting materials in the natural system, is isolated.

As used herein, the term "recombinant" means that the extended cDNA is adjacent to "backbone" nucleic acid to which it is not adjacent in its natural environment. Additionally, to be "enriched" the extended cDNAs will represent 5% or more of the number of nucleic acid inserts in a population of nucleic acid backbone molecules. Backbone

20 molecules according to the present invention include nucleic acids such as expression vectors, self-replicating nucleic acids, viruses, integrating nucleic acids, and other vectors or nucleic acids used to maintain or manipulate a nucleic acid insert of interest. Preferably, the enriched extended cDNAs represent 15% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. More preferably, the enriched extended cDNAs represent 50% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. In a highly preferred embodiment, the enriched extended cDNAs represent 90% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. "Stringent", "moderate," and "low" hybridization conditions are as defined in Example 29.

Unless otherwise indicated, a "complementary" sequence is fully complementary. Thus, extended cDNAs encoding secreted polypeptides or fragments thereof which are present in cDNA libraries in which one or more extended cDNAs encoding secreted polypeptides or fragments thereof make up 5% or more of the number of nucleic acid inserts in the backbone molecules are "enriched recombinant extended cDNAs" as defined herein. Likewise, extended cDNAs encoding secreted polypeptides or fragments thereof which are in a population of plasmids in which one or more extended cDNAs of the present invention have been inserted such that they represent 5% or more of the number of inserts in the plasmid backbone are "enriched recombinant extended cDNAs" as defined herein. However, extended

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cDNAs encoding secreted polypeptides or fragments thereof which are in cDNA libraries in which the extended cDNAs encoding secreted polypeptides or fragments thereof constitute less than 5% of the number of nucleic acid inserts in the population of backbone molecules, such as libraries in which backbone molecules having a cDNA insert encoding a secreted polypeptide are extremely rare, are not "enriched recombinant extended cDNAs."

In particular, the present invention relates to extended cDNAs which were derived from genes encoding secreted proteins. As used herein, a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal peptides in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g. soluble proteins), or partially (e.g. receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are 10 transported across the membrane of the endoplasmic reticulum.

Extended cDNAs encoding secreted proteins may include nucleic acid sequences, called signal sequences, which encode signal puptides which direct the extracellular secretion of the proteins encoded by the extended cDNAs. Generally, the signal peptides are located at the amino termini of secreted proteins.

Secreted proteins are translated by ribosomes associated with the "rough" endoplasmic reticulum. Generally, 15 secreted proteins are co-translationally transferred to the membrane of the endoplasmic reticulum. Association of the ribosome with the endoplasmic reticulum during translation of secreted proteins is mediated by the signal peptide. The signal peptide is typically cleaved following its co-translational entry into the endoplasmic reticulum. After delivery to the endoplasmic reticulum, secreted proteins may proceed through the Golgi apparatus. In the Golgi apparatus, the proteins may undergo post-translational modification before entering secretory vesicles which transport them across the cell membrane.

The extended cDNAs of the present invention have several important applications. For example, they may be used to express the entire secreted protein which they encode. Alternatively, they may be used to express portions of the secreted protein. The portions may comprise the signal peptides encoded by the extended cDNAs or the mature proteins encoded by the extended cDNAs (i.e. the proteins generated when the signal peptide is cleaved off). The portions may also comprise polypeptides having at least 10 consecutive amino acids encoded by the extended cDNAs. Alternatively, the portions may comprise at least 15 consecutive amino acids encoded by the extended cDNAs. In some embodiments, the portions may comprise at least 25 consecutive amino acids encoded by the extended cDNAs. In other embodiments, the portions may comprise at least 40 amino acids encoded by the extended cDNAs.

Antibodies which specifically recognize the entire secreted proteins encoded by the extended cDNAs or fragments thereof having at least 10 consecutive amino acids, at least 15 consecutive amino acids, at least 25 consecutive amino acids, or at least 40 consecutive amino acids may also be obtained as described below. Antibodies which specifically recognize the mature protein generated when the signal peptide is cleaved may also be obtained as described below. Similarly, antibodies which specifically recognize the signal peptides encoded by the extended cDNAs may also be obtained.



In some embodiments, the extended cDNAs include the signal sequence. In other embodiments, the extended cDNAs may include the full coding sequence for the mature protein (i.e. the protein generated when the signal polypeptide is cleaved off). In addition, the extended cDNAs may include regulatory regions upstream of the translation start site or downstream of the stop codon which control the amount, location, or developmental stage of gene expression. As discussed above, secreted proteins are therapeutically important. Thus, the proteins expressed from the cDNAs may be useful in treating or controlling a variety of human conditions. The extended cDNAs may also be used to obtain the corresponding genomic DNA. The term "corresponding genomic DNA" refers to the genomic DNA which encodes mRNA which includes the sequence of one of the strands of the extended cDNA in which thymidine residues in the sequence of the extended cDNA are replaced by uracil residues in the mRNA.

The extended cDNAs or genomic DNAs obtained therefrom may be used in forensic procedures to identify individuals or in diagnostic procedures to identify individuals having genetic diseases resulting from abnormal expression of the genes corresponding to the extended cDNAs. In addition, the present invention is useful for constructing a high resolution map of the human chromosomes.

The present invention also relates to secretion vectors capable of directing the secretion of a protein of
interest. Such vectors may be used in gene therapy strategies in which it is desired to produce a gene product in one cell
which is to be delivered to another location in the body. Secretion vectors may also facilitate the purification of desired
proteins.

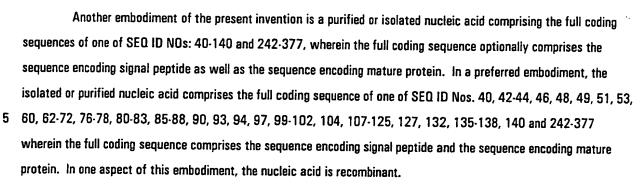
The present invention also relates to expression vectors capable of directing the expression of an inserted gene in a desired spatial or temporal manner or at a desired level. Such vectors may include sequences upstream of the extended cDNAs such as promoters or upstream regulatory sequences.

In addition, the present invention may also be used for gene therapy to control or treat genetic diseases. Signal peptides may also be fused to heterologous proteins to direct their extracellular secretion.

One embodiment of the present invention is a purified or isolated nucleic acid comprising the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary thereto. In one aspect of this embodiment, the nucleic acid is recombinant.

Another embodiment of the present invention is a purified or isolated nucleic acid comprising at least 10 consecutive bases of the sequence of one of SEQ ID NOs: 40-140 and 242-377 or one of the sequences complementary thereto. In one aspect of this embodiment, the nucleic acid comprises at least 15, 25, 30, 40, 50, 75, or 100 consecutive bases of one of the sequences of SEQ ID NOs: 40-140 and 242-377 or one of the sequences complementary thereto. The nucleic acid may be a recombinant nucleic acid.

Another embodiment of the present invention is a purified or isolated nucleic acid of at least 15 bases capable of hybridizing under stringent conditions to the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary to one of the sequences of SEQ ID NOs: 40-140 and 242-377. In one aspect of this embodiment, the nucleic acid is recombinant.



A further embodiment of the present invention is a purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40-140 and 242-377 which encode a mature protein. In a preferred embodiment, the purified or isolated nucleic acid comprises the nucleotides of one of SEQ ID NOs: 40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein. In one aspect of this embodiment, the nucleic acid is recombinant.

Yet another embodiment of the present invention is a purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40-140 and 242-377 which encode the signal peptide. In a preferred embodiment, the purified or isolated nucleic acid comprises the nucleotides of SEQ ID NOs: 40, 42-46, 48, 49, 51, 53, 57, 60, 62-73, 76-78, 80-83, 85-88, 90, 93-95, 97, 99-102, 104, 107-125, 127, 128, 130, 132, 134-140 and 242-377 which encode the signal peptide. In one aspect of this embodiment, the nucleic acid is recombinant.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of one of the sequences of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of a mature protein included in one of the sequences of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the purified or isolated nucleic acid encodes a polypeptide having the sequence of a mature protein included in one of the sequences of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of a signal peptide included in one of the sequences of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the purified or isolated nucleic acid encodes a polypeptide having the sequence of a signal peptide included in one of the sequences of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.

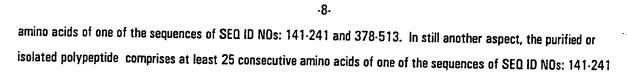
Yet another embodiment of the present invention is a purified or isolated protein comprising the sequence of one of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is a purified or isolated polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In one aspect of this embodiment, the purified or isolated polypeptide comprises at least 15, 20, 25, 35, 50, 75, 100, 150 or 200 consecutive

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and 378-513.



Another embodiment of the present invention is an isolated or purified polypeptide comprising a signal peptide of one of the polypeptides of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the isolated or purified polypeptide comprises a signal peptide of one of the polypeptides of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.

Yet another embodiment of the present invention is an isolated or purified polypeptide comprising a mature protein of one of the polypeptides of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the isolated or purified polypeptide comprises a mature protein of one of the polypeptides of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.

A further embodiment of the present invention is a method of making a protein comprising one of the sequences of SEQ ID NO: 141-241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the sequences of sequence of SEQ ID NO: 40-140 and 242-377, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the protein encoded by said cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a protein obtainable by the method described in the preceding paragraph.

Another embodiment of the present invention is a method of making a protein comprising the amino acid sequence of the mature protein contained in one of the sequences of SEQ ID NO: 141-241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the nucleotides sequence of sequence of SEQ ID NO: 40-140 and 242-377 which encode for the mature protein, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the mature protein encoded by the cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a mature protein obtainable by the method described in the preceding paragraph.

In a preferred embodiment, the above method comprises a method of making a protein comprising the amino acid sequence of the mature protein contained in one of the sequences of SEQ ID NO: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the nucleotides sequence of sequence of SEQ ID NO:

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40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode for the mature protein, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the mature protein encoded by the cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary thereto described herein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the full coding sequences of one of SEQ ID NOs: 40-140 and 242-377, wherein the full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein described herein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the nucleotides of one of SEO ID NOs: 40-140 and 242-377 which encode a mature protein which are described herein. Preferably, the host cell contains the purified or isolated nucleic acids comprising the nucleotides of one of SEO ID NOs: 40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID NOs: 40-140 and 242-377 which encode the signal peptide which are described herein. Preferably, the host cell contains the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID Nos.: 40, 42-46, 48, 49, 51, 53, 57, 60, 62-73, 76-78, 80-83, 85-88, 90, 93-95, 97, 99-102, 104, 107-125, 127, 128, 130, 132, 134-140 and 242-377 which encode the signal peptide.

Another embodiment of the present invention is a purified or isolated antibody capable of specifically binding to a protein having the sequence of one of SEQ ID NOs: 141-241 and 378-513. In one aspect of this embodiment, the antibody is capable of binding to a polypeptide comprising at least 10 consecutive amino acids of the sequence of one of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is an array of cDNAs or fragments thereof of at least 15 nucleotides in length which includes at least one of the sequences of SEQ ID NOs: 40-140 and 242-377, or one of the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or a fragment thereof of at least 15 consecutive nucleotides. In one aspect of this embodiment, the array includes at least two of the sequences of SEQ ID NOs: 40-140 and 242-377, or fragments thereof of at least 15 consecutive nucleotides. In another aspect of this embodiment, the array includes at least five of the sequences of SEQ ID NOs: 40-140 and 242-377, the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or fragments thereof of at least 15 consecutive nucleotides.



A further embodiment of the invention encompasses purified polynucleotides comprising an insert from a clone deposited in a deposit having an accession number selected from the group consisting of the accession numbers listed in Table VI or a fragment thereof comprising a contiguous span of at least 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 nucleotides of said insert. An additional embodiment of the invention encompasses purified polypeptides which comprise, consist of, or consist essentially of an amino acid sequence encoded by the insert from a clone deposited in a deposit having an accession number selected from the group consisting of the accession numbers listed in Table VI, as well as polypeptides which comprise a fragment of said amino acid sequence consisting of a signal peptide, a mature protein, or a contiguous span of at least 5, 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 amino acids encoded by said insert.

An additional embodiment of the invention encompasses purified polypeptides which comprise a contiguous span of at least 5, 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 amino acids of SEQ ID NOs: 158, 174, 175, 196, 226, 231, 232, wherein said contiguous span comprises at least one of the amino acid positions which was not shown to be identical to a public sequence in any of Figures 11 to 15. Also encompassed by the invention are purified polynuculeotides encoding said polypeptides.

### **Brief Description of the Drawings**

Figure 1 is a summary of a procedure for obtaining cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived.

Figure 2 is an analysis of the 43 amino terminal amino acids of all human SwissProt proteins to determine the frequency of false positives and false negatives using the techniques for signal peptide identification described herein.

Figure 3 shows the distribution of von Heijne scores for 5' ESTs in each of the categories described herein and the probability that these 5' ESTs encode a signal peptide.

Figure 4 shows the distribution of 5' ESTs in each category and the number of 5' ESTs in each category having a given minimum von Heijne's score.

Figure 5 shows the tissues from which the mRNAs corresponding to the 5' ESTs in each of the categories described herein were obtained.

Figure 6 illustrates a method for obtaining extended cDNAs.

Figure 7 is a map of pED6dpc2. pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SSt cDNAs are cloned between EcoRI and NotI. PED vectors are described in Kaufman et al. 30 (1991), NAR 19: 4485-4490.

Figure 8 provides a schematic description of the promoters isolated and the way they are assembled with the corresponding 5' tags.

Figure 9 describes the transcription factor binding sites present in each of these promoters.

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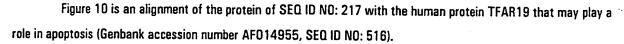


Figure 11 is an alignment of the proteins of SEQ ID NOs: 174, 175 and 232 with a human secreted protein (Genseq accession number W36955, SEQ ID NO: 517).

Figure 12 is an alignment of the protein of SEQ ID NO: 231 with the human E25 protein (Genbank accession number AF038953, SEQ ID NO: 515).

Figure 13 is an alignment of the protein of SEQ ID NO: 196 with the human seventransmembrane protein (Genbank accession number Y11395, SEQ ID NO: 518).

Figure 14 is an alignment of the protein of SEQ ID NOs: 158 with the murine subunit 7a of the COP9 complex (Genbank accession number AF071316, SEQ ID NO: 519).

Figure 15 is an alignment of the protein of SEQ ID NO: 226 with the bovine subunit B14.5B of the NADH-ubiquinone oxidureductase complex (Arizmendi *et al, FEBS Lett.*, **313**: 80-84 (1992) and Swissprot accession -number Q02827, SEQ ID NO: 514).

### **Detailed Description of the Preferred Embodiment**

### 15 I. Obtaining 5' ESTs

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The present extended cDNAs were obtained using 5' ESTs which were isolated as described below.

### A. Chemical Methods for Obtaining mRNAs having Intact 5' Ends

In order to obtain the 5' ESTs used to obtain the extended cDNAs of the present invention, mRNAs having intact 5' ends must be obtained. Currently, there are two approaches for obtaining such mRNAs. One of these 20 approaches is a chemical modification method involving derivatization of the 5' ends of the mRNAs and selection of the derivatized mRNAs. The 5' ends of eucaryotic mRNAs possess a structure referred to as a "cap" which comprises a guanosine methylated at the 7 position. The cap is joined to the first transcribed base of the mRNA by a 5', 5'. triphosphate bond. In some instances, the 5' guanosine is methylated in both the 2 and 7 positions. Rarely, the 5' guanosine is trimethylated at the 2, 7 and 7 positions. In the chemical method for obtaining mRNAs having intact 5' 25 ends, the 5' cap is specifically derivatized and coupled to a reactive group on an immobilizing substrate. This specific derivatization is based on the fact that only the ribose linked to the methylated guanosine at the 5' end of the mRNA and the ribose linked to the base at the 3' terminus of the mRNA, possess 2', 3'-cis diols. Optionally, where the 3' terminal ribose has a 2', 3'-cis diol, the 2', 3'-cis diol at the 3' end may be chemically modified, substituted, converted, or eliminated, leaving only the ribose linked to the methylated guanosine at the 5' end of the mRNA with a 2', 3'-cis diol. A 30 variety of techniques are available for eliminating the 2', 3'-cis diol on the 3' terminal ribose. For example, controlled alkaline hydrolysis may be used to generate mRNA fragments in which the 3' terminal ribose is a 3'-phosphate, 2'phosphate or (2', 3')-cyclophosphate. Thereafter, the fragment which includes the original 3' ribose may be eliminated from the mixture through chromatography on an oligo-dT column. Alternatively, a base which lacks the 2', 3'-cis diol

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may be added to the 3' end of the mRNA using an RNA ligase such as T4 RNA ligase. Example 1 below describes a method for ligation of pCp to the 3' end of messenger RNA.

#### **EXAMPLE 1**

# Ligation of the Nucleoside Diphosphate pCp to the 3' End of Messenger RNA

1  $\mu g$  of RNA was incubated in a final reaction medium of 10  $\mu l$  in the presence of 5 U of  $T_4$  phage RNA ligase in the buffer provided by the manufacturer (Gibco - BRL), 40 U of the RNase inhibitor RNasin (Promega) and, 2  $\mu l$  of  $^{32}$ pCp (Amersham #PB 10208).

The incubation was performed at 37°C for 2 hours or overnight at 7-8°C.

Following modification or elimination of the 2', 3'-cis diol at the 3' ribose, the 2', 3'-cis diol present at the 5' end of the mRNA may be oxidized using reagents such as NaBH<sub>4</sub>, NaBH<sub>3</sub>CN, or sodium periodate, thereby converting the 2', 3'-cis diol to a dialdehyde. Example 2 describes the oxidation of the 2', 3'-cis diol at the 5' end of the mRNA with sodium periodate.

#### **EXAMPLE 2**

### Oxidation of 2', 3'-cis diol at the 5' End of the mRNA

- 0.1 OD unit of either a capped oligoribonucleotide of 47 nucleotides (including the cap) or an uncapped oligoribonucleotide of 46 nucleotides were treated as follows. The oligoribonucleotides were produced by in vitro transcription using the transcription kit "AmpliScribe T7" (Epicentre Technologies). As indicated below, the DNA template for the RNA transcript contained a single cytosine. To synthesize the uncapped RNA, all four NTPs were included in the in vitro transcription reaction. To obtain the capped RNA, GTP was replaced by an analogue of the cap, m7G(5')ppp(5')G. This compound, recognized by polymerase, was incorporated into the 5' end of the nascent transcript during the step of initiation of transcription but was not capable of incorporation during the extension step. Consequently, the resulting RNA contained a cap at its 5' end. The sequences of the oligoribonucleotides produced by the in vitro transcription reaction were:
  - +Cap:
- 25 5'm7GpppGCAUCCUACUCCCAUCCAAUUCCACCCUAACUCCUCCCAUCUCCAC-3' (SEQ ID NO:1)
  - -Cap:
  - 5'-pppGCAUCCUACUCCCAUCCAAUUCCACCCUAACUCCUCCCAUCUCCAC-3' (SEQ ID NO:2)

The oligoribonucleotides were dissolved in 9 µl of acetate buffer (0.1 M sodium acetate, pH 5.2) and 3 µl of freshly prepared 0.1 M sodium periodate solution. The mixture was incubated for 1 hour in the dark at 4°C or room temperature. Thereafter, the reaction was stopped by adding 4 µl of 10% ethylene glycol. The product was ethanol precipitated, resuspended in 10µl or more of water or appropriate buffer and dialyzed against water.

The resulting aldehyde groups may then be coupled to molecules having a reactive amine group, such as hydrazine, carbazide, thiocarbazide or semicarbazide groups, in order to facilitate enrichment of the 5' ends of the mRNAs. Molecules having reactive amine groups which are suitable for use in selecting mRNAs having intact 5' ends

include avidin, proteins, antibodies, vitamins, ligands capable of specifically binding to receptor molecules, or oligonucleotides. Example 3 below describes the coupling of the resulting dialdehyde to biotin.

#### **EXAMPLE 3**

### Coupling of the Dialdehyde with Biotin

The oxidation product obtained in Example 2 was dissolved in 50 μl of sodium acetate at a pH of between 5 and 5.2 and 50 μl of freshly prepared 0.02 M solution of biotin hydrazide in a methoxyethanol/water mixture (1:1) of formula:

In the compound used in these experiments, n=5. However, it will be appreciated that other commercially available hydrazides may also be used, such as molecules of the formula above in which n varies from 0 to 5.

The mixture was then incubated for 2 hours at 37°C. Following the incubation, the mixture was precipitated with ethanol and dialyzed against distilled water.

Example 4 demonstrates the specificity of the biotinylation reaction.

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#### **EXAMPLE 4**

### Specificity of Biotinylation

The specificity of the biotinylation for capped mRNAs was evaluated by gel electrophoresis of the following samples:

- Sample 1. The 46 nucleotide uncapped in vitro transcript prepared as in Example 2 and labeled with <sup>32</sup>pCp as described in Example 1.
  - Sample 2. The 46 nucleotide uncapped in vitro transcript prepared as in Example 2, labeled with <sup>32</sup>pCp as described in Example 1, treated with the oxidation reaction of Example 2, and subjected to the biotinylation conditions of Example 3.
- Sample 3. The 47 nucleotide capped in vitro transcript prepared as in Example 2 and labeled with  $^{32}$ pCp as described in Example 1.
  - Sample 4. The 47 nucleotide capped in vitro transcript prepared as in Example 2, labeled with  $^{32}pCp$  as described in Example 1, treated with the oxidation reaction of Example 2, and subjected to the biotinylation conditions of Example 3.
- Samples 1 and 2 had indentical migration rates, demonstrating that the uncapped RNAs were not oxidized and 30 biotinylated. Sample 3 migrated more slowly than Samples 1 and 2, while Sample 4 exhibited the slowest migration.



The difference in migration of the RNAs in Samples 3 and 4 demonstrates that the capped RNAs were specifically biotinylated.

In some cases, mRNAs having intact 5' ends may be enriched by binding the molecule containing a reactive amine group to a suitable solid phase substrate such as the inside of the vessel containing the mRNAs, magnetic beads, chromatography matrices, or nylon or nitrocellulose membranes. For example, where the molecule having a reactive amine group is biotin, the solid phase substrate may be coupled to avidin or streptavidin. Alternatively, where the molecule having the reactive amine group is an antibody or receptor ligand, the solid phase substrate may be coupled to the cognate antigen or receptor. Finally, where the molecule having a reactive amine group comprises an oligonucleotide, the solid phase substrate may comprise a complementary oligonucleotide.

The mRNAs having intact 5' ends may be released from the solid phase following the enrichment procedure.

For example, where the dialdehyde is coupled to biotin hydrazide and the solid phase comprises streptavidin, the mRNAs may be released from the solid phase by simply heating to 95 degrees Celsius in 2% SDS. In some methods, the molecule having a reactive amine group may also be cleaved from the mRNAs having intact 5' ends following enrichment.

Example 5 describes the capture of biotinylated mRNAs with streptavidin coated beads and the release of the biotinylated mRNAs from the beads following enrichment.

#### **EXAMPLE 5**

# Capture and Release of Biotinylated mRNAs Using Strepatividin Coated Beads

The streptavidin-coated magnetic beads were prepared according to the manufacturer's instructions (CPG Inc., USA). The biotinylated mRNAs were added to a hybridization buffer (1.5 M NaCl, pH 5 · 6). After incubating for 30 minutes, the unbound and nonbiotinylated material was removed. The beads were washed several times in water with 1% SDS. The beads obtained were incubated for 15 minutes at 95°C in water containing 2% SDS.

Example 6 demonstrates the efficiency with which biotinylated mRNAs were recovered from the streptavidin coated beads.

#### **EXAMPLE 6**

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### Efficiency of Recovery of Biotinylated mRNAs

The efficiency of the recovery procedure was evaluated as follows. RNAs were labeled with <sup>32</sup>pCp, oxidized, biotinylated and bound to streptavidin coated beads as described above. Subsequently, the bound RNAs were incubated for 5, 15 or 30 minutes at 95°C in the presence of 2% SDS.

The products of the reaction were analyzed by electrophoresis on 12% polyacrylamide gels under denaturing conditions (7 M urea). The gels were subjected to autoradiography. During this manipulation, the hydrazone bonds were not reduced.

Increasing amounts of nucleic acids were recovered as incubation times in 2% SDS increased, demonstrating that biotinylated mRNAs were efficiently recovered.

In an alternative method for obtaining mRNAs having intact 5' ends, an oligonucleotide which has been derivatized to contain a reactive amine group is specifically coupled to mRNAs having an intact cap. Preferably, the 3' end of the mRNA is blocked prior to the step in which the aldehyde groups are joined to the derivatized oligonucleotide, as described above, so as to prevent the derivatized oligonucleotide from being joined to the 3' end of the mRNA. For example, pCp may be attached to the 3' end of the mRNA using T4 RNA ligase. However, as discussed above, blocking the 3' end of the mRNA is an optional step. Derivatized oligonucleotides may be prepared as described below in Example 7.

#### **EXAMPLE 7**

### **Derivatization of the Oligonucleotide**

An oligonucleotide phosphorylated at its 3' end was converted to a 3' hydrazide in 3' by treatment with an aqueous solution of hydrazine or of dihydrazide of the formula  $H_2N(R1)NH_2$  at about 1 to 3 M, and at pH 4.5, in the presence of a carbodiimide type agent soluble in water such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide at a final concentration of 0.3 M at a temperature of 8°C overnight.

The derivatized oligonucleotide was then separated from the other agents and products using a standard technique for isolating oligonucleotides.

As discussed above, the mRNAs to be enriched may be treated to eliminate the 3' OH groups which may be present thereon. This may be accomplished by enzymatic ligation of sequences lacking a 3' OH, such as pCp, as described above in Example 1. Alternatively, the 3' OH groups may be eliminated by alkaline hydrolysis as described in Example 8 below.

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### **EXAMPLE 8**

### Alkaline Hydrolysis of mRNA

The mRNAs may be treated with alkaline hydrolysis as follows. In a total volume of  $100\mu$ l of 0.1N sodium hydroxide, 1.5 $\mu$ g mRNA is incubated for 40 to 60 minutes at 4°C. The solution is neutralized with acetic acid and precipitated with ethanol.

Following the optional elimination of the 3' OH groups, the diol groups at the 5' ends of the mRNAs are oxidized as described below in Example 9.

### **EXAMPLE 9**

#### **Oxidation of Diols**

Up to 1 OD unit of RNA was dissolved in 9 µl of buffer (0.1 M sodium acetate, pH 6-7 or water) and 3 µl of freshly prepared 0.1 M sodium periodate solution. The reaction was incubated for 1 h in the dark at 4°C or room temperature. Following the incubation, the reaction was stopped by adding 4 µl of 10% ethylene glycol. Thereafter the mixture was incubated at room temperature for 15 minutes. After ethanol precipitation, the product was resuspended in 10µl or more of water or appropriate buffer and dialyzed against water.





Following oxidation of the diol groups at the 5' ends of the mRNAs, the derivatized oligonucleotide was joined to the resulting aldehydes as described in Example 10.

### **EXAMPLE 10**

# Reaction of Aldehydes with Derivatized Oligonucleotides

The oxidized mRNA was dissolved in an acidic medium such as 50 µl of sodium acetate pH 4-6. 50 µl of a solution of the derivatized oligonucleotide was added such that an mRNA:derivatized oligonucleotide ratio of 1:20 was obtained and mixture was reduced with a borohydride. The mixture was allowed to incubate for 2 h at 37°C or overnight (14 h) at 10°C. The mixture was ethanol precipitated, resuspended in 10µl or more of water or appropriate buffer and dialyzed against distilled water. If desired, the resulting product may be analyzed using acrylamide gel electrophoresis, HPLC analysis, or other conventional techniques.

Following the attachment of the derivatized oligonucleotide to the mRNAs, a reverse transcription reaction may be performed as described in Example 11 below.

#### **EXAMPLE 11**

### Reverse Transcription of mRNAs

An oligodeoxyribonucleotide was derivatized as follows. 3 OD units of an oligodeoxyribonucleotide of sequence ATCAAGAATTCGCACGAGACCATTA (SEQ ID NO:3) having 5'-OH and 3'-P ends were dissolved in 70 μl of a 1.5 M hydroxybenzotriazole solution, pH 5.3, prepared in dimethylformamide/water (75:25) containing 2 μg of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. The mixture was incubated for 2 h 30 min at 22°C. The mixture was then precipitated twice in LiClO<sub>4</sub>/acetone. The pellet was resuspended in 200 μl of 0.25 M hydrazine and incubated at 8°C from 3 to 14 h. Following the hydrazine reaction, the mixture was precipitated twice in LiClO<sub>4</sub>/acetone.

The messenger RNAs to be reverse transcribed were extracted from blocks of placenta having sides of 2 cm which had been stored at -80°C. The mRNA was extracted using conventional acidic phenol techniques. Oligo-dT chromatography was used to purify the mRNAs. The integrity of the mRNAs was checked by Northern-blotting.

The diol groups on 7 µg of the placental mRNAs were oxidized as described above in Example 9. The

derivatized oligonucleotide was joined to the mRNAs as described in Example 10 above except that the precipitation step was replaced by an exclusion chromatography step to remove derivatized oligodeoxyribonucleotides which were not joined to mRNAs. Exclusion chromatography was performed as follows:

10 ml of AcA34 (BioSepra#230151) gel were equilibrated in 50 ml of a solution of 10 mM Tris pH 8.0, 300 mM NaCl, 1 mM EDTA, and 0.05% SDS. The mixture was allowed to sediment. The supernatant was eliminated and the gel was resuspended in 50 ml of buffer. This procedure was repeated 2 or 3 times.

A glass bead (diameter 3 mm) was introduced into a 2 ml disposable pipette (length 25 cm). The pipette was filled with the gel suspension until the height of the gel stabilized at 1 cm from the top of the pipette. The column was then equilibrated with 20 ml of equilibration buffer (10 mM Tris HCl pH 7.4, 20 mM NaCl).



10  $\mu$ l of the mRNA which had been reacted with the derivatized oligonucleotide were mixed in 39  $\mu$ l of 10 mM urea and 2  $\mu$ l of blue-glycerol buffer, which had been prepared by dissolving 5 mg of bromophenol blue in 60% glycerol (v/v), and passing the mixture through a filter with a filter of diameter 0.45  $\mu m$ .

The column was loaded. As soon as the sample had penetrated, equilibration buffer was added. 100  $\mu l$ 5 fractions were collected. Derivatized oligonucleotide which had not been attached to mRNA appeared in fraction 16 and later fractions. Fractions 3 to 15 were combined and precipitated with ethanol.

The mRNAs which had been reacted with the derivatized oligonucleotide were spotted on a nylon membrane and hybridized to a radioactive probe using conventional techniques. The radioactive probe used in these hybridizations was an oligodeoxyribonucleotide of sequence TAATGGTCTCGTGCGAATTCTTGAT (SEQ ID NO:4) which was 10 anticomplementary to the derivatized oligonucleotide and was labeled at its 5' end with 32P. 1/10th of the mRNAs which had been reacted with the derivatized oligonucleotide was spotted in two spots on the membrane and the membrane was visualized by autoradiography after hybridization of the probe. A signal was observed, indicating that the derivatized oligonucleotide had been joined to the mRNA.

The remaining 9/10 of the mRNAs which had been reacted with the derivatized oligonucleotide was reverse 15 transcribed as follows. A reverse transcription reaction was carried out with reverse transcriptase following the manufacturer's instructions. To prime the reaction, 50 pmol of nonamers with random sequence were used.

A portion of the resulting cDNA was spotted on a positively charged nylon membrane using conventional methods. The cDNAs were spotted on the membrane after the cDNA:RNA heteroduplexes had been subjected to an alkaline hydrolysis in order to eliminate the RNAs. An oligonucleotide having a sequence identical to that of the derivatized 20 oligonucleotide was labeled at its 5' end with 32P and hybridized to the cDNA blots using conventional techniques. Single-stranded cDNAs resulting from the reverse transcription reaction were spotted on the membrane. As controls, the blot contained 1 pmol, 100 fmol, 50 fmol, 10 fmol and 1 fmol respectively of a control oligodeoxyribonucleotide of sequence identical to that of the derivatized oligonucleotide. The signal observed in the spots containing the cDNA indicated that approximately 15 fmol of the derivatized oligonucleotide had been reverse transcribed.

These results demonstrate that the reverse transcription can be performed through the cap and, in particular, that reverse transcriptase crosses the 5'-P-P-5' bond of the cap of eukaryotic messenger RNAs.

The single stranded cDNAs obtained after the above first strand synthesis were used as template for PCR reactions. Two types of reactions were carried out. First, specific amplification of the mRNAs for the alpha globin, dehydrogenase, pp15 and elongation factor E4 were carried out using the following pairs of oligodeoxyribonucleotide primers.

alpha-globin

GLO-S: CCG ACA AGA CCA ACG TCA AGG CCG C (SEQ ID NO:5)

GLO-As: TCA CCA GCA GGC AGT GGC TTA GGA G 3' (SEO ID NO:6)

dehydrogenase

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3 DH-S: AGT GAT TCC TGC TAC TTT GGA TGG C (SEQ ID NO:7)

3 DH-As: GCT TGG TCT TGT TCT GGA GTT TAG A (SEQ ID NO:8)

pp15

PP15-S: TCC AGA ATG GGA GAC AAG CCA ATT T (SEQ ID NO:9)

5 PP15-As: AGG GAG GAG GAA ACA GCG TGA GTC C (SEQ ID NO:10)

Elongation factor E4

EFA1-S: ATG GGA AAG GAA AAG ACT CAT ATC A (SEQ ID NO:11)

EF1A-As: AGC AGC AAC AAT CAG GAC AGC ACA G (SEQ ID NO:12)

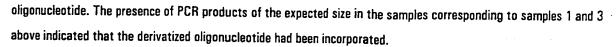
Non specific amplifications were also carried out with the antisense (\_As) oligodeoxyribonucleotides of the pairs described above and a primer chosen from the sequence of the derivatized oligodeoxyribonucleotide (ATCAAGAATTCGCACGAGACCATTA) (SEQ ID NO:13).

A 1.5% agarose gel containing the following samples corresponding to the PCR products of reverse transcription was stained with ethidium bromide. (1/20th of the products of reverse transcription were used for each PCR reaction).

- Sample 1: The products of a PCR reaction using the globin primers of SEQ ID NOs 5 and 6 in the presence of cDNA.
  - Sample 2: The products of a PCR reaction using the globin primers of SEQ ID NOs 5 and 6 in the absence of added cDNA.
- Sample 3: The products of a PCR reaction using the dehydrogenase primers of SEQ ID NOs 7 and 8 in the presence of cDNA.
  - Sample 4: The products of a PCR reaction using the dehydrogenase primers of SEQ ID NOs 7 and 8 in the absence of added cDNA.
  - Sample 5: The products of a PCR reaction using the pp15 primers of SEQ ID NOs 9 and 10 in the presence of cDNA.
- Sample 6: The products of a PCR reaction using the pp15 primers of SEQ ID NOs 9 and 10 in the absence of added cDNA.
  - Sample 7: The products of a PCR reaction using the EIE4 primers of SEQ ID NOs 11 and 12 in the presence of added cDNA.
- Sample 8: The products of a PCR reaction using the EIE4 primers of SEQ ID NOs 11 and 12 in the absence of 30 added cDNA.

In Samples 1, 3, 5 and 7, a band of the size expected for the PCR product was observed, indicating the presence of the corresponding sequence in the cDNA population.

PCR reactions were also carried out with the antisense oligonucleotides of the globin and dehydrogenase primers (SEQ ID NOs 6 and 8) and an oligonucleotide whose sequence corresponds to that of the derivatized



The above examples summarize the chemical procedure for enriching mRNAs for those having intact 5' ends.

Further detail regarding the chemical approaches for obtaining mRNAs having intact 5' ends are disclosed in

International Application No. W096/34981, published November 7, 1996.

Strategies based on the above chemical modifications to the 5' cap structure may be utilized to generate cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived. In one version of such procedures, the 5' ends of the mRNAs are modified as described above. Thereafter, a reverse transcription reaction is conducted to extend a primer complementary to the mRNA to the 5' end of the mRNA. Single stranded RNAs are eliminated to obtain a population of cDNA/mRNA heteroduplexes in which the mRNA includes an intact 5' end. The resulting heteroduplexes may be captured on a solid phase coated with a molecule capable of interacting with the molecule used to derivatize the 5' end of the mRNA. Thereafter, the strands of the heteroduplexes are separated to recover single stranded first cDNA strands which include the 5' end of the mRNA. Second strand cDNA synthesis may then proceed using conventional techniques. For example, the procedures disclosed in WO 96/34981 or in Carninci, P. et al. High-Efficiency Full-Length cDNA Cloning by Biotinylated CAP Trapper. Genomics 37:327-336 (1996) may be employed to select cDNAs which include the sequence derived from the 5' end of the coding sequence of the mRNA.

Following ligation of the oligonucleotide tag to the 5' cap of the mRNA, a reverse transcription reaction is conducted to extend a primer complementary to the mRNA to the 5' end of the mRNA. Following elimination of the RNA component of the resulting heteroduplex using standard techniques, second strand cDNA synthesis is conducted with a primer complementary to the oligonucleotide tag.

Figure 1 summarizes the above procedures for obtaining cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived.

### B. Enzymatic Methods for Obtaining mRNAs having Intact 5' Ends

Other techniques for selecting cDNAs extending to the 5' end of the mRNA from which they are derived are fully enzymatic. Some versions of these techniques are disclosed in Dumas Milne Edwards J.B. (Doctoral Thesis of Paris VI University, Le clonage des ADNc complets: difficultes et perspectives nouvelles. Apports pour l'etude de la regulation de l'expression de la tryptophane hydroxylase de rat, 20 Dec. 1993), EPO 625572 and Kato et al. Construction of a Human Full-Length cDNA Bank. Gene 150:243-250 (1994).

Briefly, in such approaches, isolated mRNA is treated with alkaline phosphatase to remove the phosphate

groups present on the 5' ends of uncapped incomplete mRNAs. Following this procedure, the cap present on full length mRNAs is enzymatically removed with a decapping enzyme such as T4 polynucleotide kinase or tobacco acid pyrophosphatase. An oligonucleotide, which may be either a DNA oligonucleotide or a DNA-RNA hybrid oligonucleotide having RNA at its 3' end, is then ligated to the phosphate present at the 5' end of the decapped mRNA using T4 RNA



ligase. The oligonucleotide may include a restriction site to facilitate cloning of the cDNAs following their synthesis. Example 12 below describes one enzymatic method based on the doctoral thesis of Dumas.

#### **EXAMPLE 12**

### Enzymatic Approach for Obtaining 5' ESTs

Twenty micrograms of PolyA+ RNA were dephosphorylated using Calf Intestinal Phosphatase (Biolabs). After a phenol chloroform extraction, the cap structure of mRNA was hydrolysed using the Tobacco Acid Pyrophosphatase (purified as described by Shinshi et al., Biochemistry 15: 2185-2190, 1976) and a hemi 5'DNA/RNA-3' oligonucleotide having an unphosphorylated 5' end, a stretch of adenosine ribophosphate at the 3' end, and an EcoRI site near the 5' end was ligated to the 5'P ends of mRNA using the T4 RNA ligase (Biolabs). Oligonucleotides suitable for use in this procedure are preferably 30-50 bases in length. Oligonucleotides having an unphosphorylated 5' end may be synthesized by adding a fluorochrome at the 5' end. The inclusion of a stretch of adenosine ribophosphates at the 3' end of the oligonucleotide increases ligation efficiency. It will be appreciated that the oligonucleotide may contain cloning sites other than EcoRI.

Following ligation of the oligonucleotide to the phosphate present at the 5' end of the decapped mRNA, first
and second strand cDNA synthesis may be carried out using conventional methods or those specified in EPO 625,572
and Kato et al. Construction of a Human Full-Length cDNA Bank. Gene 150:243-250 (1994), and Dumas Milne Edwards,
supra. The resulting cDNA may then be ligated into vectors such as those disclosed in Kato et al. Construction of a
Human Full-Length cDNA Bank. Gene 150:243-250 (1994) or other nucleic acid vectors known to those skilled in the art
using techniques such as those described in Sambrook et al., Molecular Cloning: A Laboratory Manual 2d Ed., Cold
Spring Harbor Laboratory Press, 1989.

#### II. Characterization of 5' ESTs

The above chemical and enzymatic approaches for enriching mRNAs having intact 5' ends were employed to obtain 5' ESTs. First, mRNAs were prepared as described in Example 13 below.

#### **EXAMPLE 13**

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#### Preparation of mRNA

Total human RNAs or PolyA+ RNAs derived from 29 different tissues were respectively purchased from LABIMO and CLONTECH and used to generate 44 cDNA libraries as described below. The purchased RNA had been isolated from cells or tissues using acid guanidium thiocyanate-phenol-chloroform extraction (Chomczyniski, P and Sacchi, N., Analytical Biochemistry 162:156-159, 1987). PolyA+ RNA was isolated from total RNA (LABIMO) by two passes of oligodT chromatography, as described by Aviv and Leder (Aviv, H. and Leder, P., Proc. Natl. Acad. Sci. USA 69:1408-1412, 1972) in order to eliminate ribosomal RNA.

The quality and the integrity of the poly A+ were checked. Northern blots hybridized with a globin probe were used to confirm that the mRNAs were not degraded. Contamination of the PolyA+ mRNAs by ribosomal sequences was checked using RNAs blots and a probe derived from the sequence of the 28S RNA. Preparations of mRNAs with less



PCT/IB98/02122

than 5% of ribosomal RNAs were used in library construction. To avoid constructing libraries with RNAs contaminated by exogenous sequences (prokaryotic or fungal), the presence of bacterial 16S ribosomal sequences or of two highly expressed mRNAs was examined using PCR.

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Following preparation of the mRNAs, the above described chemical and/or the enzymatic procedures for 5 enriching mRNAs having intact 5' ends discussed above were employed to obtain 5' ESTs from various tissues. In both approaches an oligonucleotide tag was attached to the cap at the 5' ends of the mRNAs. The oligonucleotide tag had an EcoRI site therein to facilitate later cloning procedures.

Following attachment of the oligonucleotide tag to the mRNA by either the chemical or enzymatic methods, the integrity of the mRNA was examined by performing a Northern blot with 200-500ng of mRNA using a probe 10 complementary to the oligonucleotide tag.

#### **EXAMPLE 14**

### cDNA Synthesis Using mRNA Templates Having Intact 5' Ends

For the mRNAs joined to oligonucleotide tags using both the chemical and enzymatic methods, first strand cDNA synthesis was performed using reverse transcriptase with random nonamers as primers. In order to protect 15 internal EcoRI sites in the cDNA from digestion at later steps in the procedure, methylated dCTP was used for first strand synthesis. After removal of RNA by an alkaline hydrolysis, the first strand of cDNA was precipitated using isopropanol in order to eliminate residual primers.

For both the chemical and the enzymatic methods, the second strand of the cDNA was synthesized with a Klenow fragment using a primer corresponding to the 5'end of the ligated oligonucleotide described in Example 12. Preferably, the primer is 20-25 bases in length. Methylated dCTP was also used for second strand synthesis in order to protect internal EcoRI sites in the cDNA from digestion during the cloning process.

Following cDNA synthesis, the cDNAs were cloned into pBlueScript as described in Example 15 below.

#### **EXAMPLE 15**

### Insertion of cDNAs into BlueScript

Following second strand synthesis, the ends of the cDNA were blunted with T4 DNA polymerase (Biolabs) and 25 the cDNA was digested with EcoRI. Since methylated dCTP was used during cDNA synthesis, the EcoRI site present in the tag was the only site which was hemi-methylated. Consequently, only the EcoRI site in the oligonucleotide tag was susceptible to EcoRI digestion. The cDNA was then size fractionated using exclusion chromatography (AcA, Biosepra). Fractions corresponding to cDNAs of more than 150 bp were pooled and ethanol precipitated. The cDNA was directionally cloned into the Smal and EcoRI ends of the phagemid pBlueScript vector (Stratagene). The ligation mixture was electroporated into bacteria and propagated under appropriate antibiotic selection.

Clones containing the oligonucleotide tag attached were selected as described in Example 16 below.

### **EXAMPLE 16**

Selection of Clones Having the Oligonucleotide Tag Attached Thereto



The plasmid DNAs containing 5' EST libraries made as described above were purified (Qiagen). A positive selection of the tagged clones was performed as follows. Briefly, in this selection procedure, the plasmid DNA was converted to single stranded DNA using gene II endonuclease of the phage F1 in combination with an exonuclease (Chang et al., Gene 127:95-8, 1993) such as exonuclease III or T7 gene 6 exonuclease. The resulting single stranded DNA was then purified using paramagnetic beads as described by Fry et al., Biotechniques, 13: 124-131, 1992. In this procedure, the single stranded DNA was hybridized with a biotinylated oligonucleotide having a sequence corresponding to the 3' end of the oligonucleotide described in Example 13. Preferably, the primer has a length of 20-25 bases. Clones including a sequence complementary to the biotinylated oligonucleotide were captured by incubation with streptavidin coated magnetic beads followed by magnetic selection. After capture of the positive clones, the plasmid DNA was released from the magnetic beads and converted into double stranded DNA using a DNA polymerase such as the ThermoSequenase obtained from Amersham Pharmacia Biotech. Alternatively, protocols such as the Gene Trapper kit (Gibco BRL) may be used. The double stranded DNA was then electroporated into bacteria. The percentage of positive clones having the 5' tag oligonucleotide was estimated to typically rank between 90 and 98% using dot blot analysis.

Following electroporation, the libraries were ordered in 384-microtiter plates (MTP). A copy of the MTP was stored for future needs. Then the libraries were transferred into 96 MTP and sequenced as described below.

### **EXAMPLE 17**

### Sequencing of Inserts in Selected Clones

Plasmid inserts were first amplified by PCR on PE 9600 thermocyclers (Perkin-Elmer), using standard SETA-A and SETA-B primers (Genset SA), AmpliTaqGold (Perkin-Elmer), dNTPs (Boehringer), buffer and cycling conditions as recommended by the Perkin-Elmer Corporation.

PCR products were then sequenced using automatic ABI Prism 377 sequencers (Perkin Elmer, Applied Biosystems Division, Foster City, CA). Sequencing reactions were performed using PE 9600 thermocyclers (Perkin Elmer) with standard dye-primer chemistry and ThermoSequenase (Amersham Life Science). The primers used were either T7 or 21M13 (available from Genset SA) as appropriate. The primers were labeled with the JOE, FAM, ROX and TAMRA dyes. The dNTPs and ddNTPs used in the sequencing reactions were purchased from Boehringer. Sequencing buffer, reagent concentrations and cycling conditions were as recommended by Amersham.

Following the sequencing reaction, the samples were precipitated with EtOH, resuspended in formamide loading buffer, and loaded on a standard 4% acrylamide gel. Electrophoresis was performed for 2.5 hours at 3000V on an ABI 377 sequencer, and the sequence data were collected and analyzed using the ABI Prism DNA Sequencing Analysis Software, version 2.1.2.

The sequence data from the 44 cDNA libraries made as described above were transferred to a proprietary database, where quality control and validation steps were performed. A proprietary base-caller ("Trace"), working using a Unix system automatically flagged suspect peaks, taking into account the shape of the peaks, the inter-peak resolution, and the noise level. The proprietary base-caller also performed an automatic trimming. Any stretch of 25 or

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fewer bases having more than 4 suspect peaks was considered unreliable and was discarded. Sequences corresponding to cloning vector or ligation oligonucleotides were automatically removed from the EST sequences. However, the resulting EST sequences may contain 1 to 5 bases belonging to the above mentioned sequences at their 5' end. If needed, these can easily be removed on a case by case basis.

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Thereafter, the sequences were transferred to the proprietary NETGENE™ Database for further analysis as described below.

Following sequencing as described above, the sequences of the 5' ESTs were entered in a proprietary database called NETGENETM for storage and manipulation. It will be appreciated by those skilled in the art that the data could be stored and manipulated on any medium which can be read and accessed by a computer. Computer readable media include magnetically readable media, optically readable media, or electronically readable media. For example, the computer readable media may be a hard disc, a floppy disc, a magnetic tape, CD-ROM, RAM, or ROM as well as other types of other media known to those skilled in the art.

In addition, the sequence data may be stored and manipulated in a variety of data processor programs in a variety of formats. For example, the sequence data may be stored as text in a word processing file, such as

MicrosoftWORD or WORDPERFECT or as an ASCII file in a variety of database programs familiar to those of skill in the art, such as DB2, SYBASE, or ORACLE.

The computer readable media on which the sequence information is stored may be in a personal computer, a network, a server or other computer systems known to those skilled in the art. The computer or other system preferably includes the storage media described above, and a processor for accessing and manipulating the sequence data.

Once the sequence data has been stored it may be manipulated and searched to locate those stored sequences which contain a desired nucleic acid sequence or which encode a protein having a particular functional domain. For example, the stored sequence information may be compared to other known sequences to identify homologies, motifs implicated in biological function, or structural motifs.

Programs which may be used to search or compare the stored sequences include the MacPattern (EMBL),

25 BLAST, and BLAST2 program series (NCBI), basic local alignment search tool programs for nucleotide (BLASTN) and
peptide (BLASTX) comparisons (Altschul et al, J. Mol. Biol. 215: 403 (1990)) and FASTA (Pearson and Lipman, Proc.
Natl. Acad. Sci. USA, 85: 2444 (1988)). The BLAST programs then extend the alignments on the basis of defined
match and mismatch criteria.

Motifs which may be detected using the above programs include sequences encoding leucine zippers, helix-turn
helix motifs, glycosylation sites, ubiquitination sites, alpha helices, and beta sheets, signal sequences encoding signal peptides which direct the secretion of the encoded proteins, sequences implicated in transcription regulation such as homeoboxes, acidic stretches, enzymatic active sites, substrate binding sites, and enzymatic cleavage sites.



Before searching the cDNAs in the NETGENE™ database for sequence motifs of interest, cDNAs derived from mRNAs which were not of interest were identified and eliminated from further consideration as described in Example 18 below.

### **EXAMPLE 18**

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### Elimination of Undesired Sequences from Further Consideration

5' ESTs in the NETGENE™ database which were derived from undesired sequences such as transfer RNAs, ribosomal RNAs, mitochondrial RNAs, procaryotic RNAs, fungal RNAs, Alu sequences, L1 sequences, or repeat sequences were identified using the FASTA and BLASTN programs with the parameters listed in Table II.

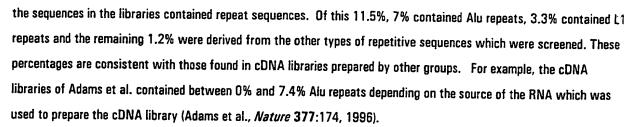
To eliminate 5' ESTs encoding tRNAs from further consideration, the 5' EST sequences were compared to the 10 sequences of 1190 known tRNAs obtained from EMBL release 38, of which 100 were human. The comparison was performed using FASTA on both strands of the 5' ESTs. Sequences having more than 80% homology over more than 60 nucleotides were identified as tRNA. Of the 144,341 sequences screened, 26 were identified as tRNAs and eliminated from further consideration.

To eliminate 5' ESTs encoding rRNAs from further consideration, the 5' EST sequences were compared to the 15 sequences of 2497 known rRNAs obtained from EMBL release 38, of which 73 were human. The comparison was performed using BLASTN on both strands of the 5' ESTs with the parameter S = 108. Sequences having more than 80%homology over stretches longer than 40 nucleotides were identified as rRNAs. Of the 144,341 sequences screened, 3,312 were identified as rRNAs and eliminated from further consideration.

To eliminate 5' ESTs encoding mtRNAs from further consideration, the 5' EST sequences were compared to the sequences of the two known mitochondrial genomes for which the entire genomic sequences are available and all sequences transcribed from these mitochondrial genomes including tRNAs, rRNAs, and mRNAs for a total of 38 sequences. The comparison was performed using BLASTN on both strands of the 5' ESTs with the parameter S = 108. Sequences having more than 80% homology over stretches longer than 40 nucleotides were identified as mtRNAs. Of the 144,341 sequences screened, 6,110 were identified as mtRNAs and eliminated from further consideration.

Sequences which might have resulted from exogenous contaminants were eliminated from further consideration by comparing the 5' EST sequences to release 46 of the EMBL bacterial and fungal divisions using BLASTN with the parameter S = 144. All sequences having more than 90% homology over at least 40 nucleotides were identified as exogenous contaminants. Of the 42 cDNA libraries examined, the average percentages of procaryotic and fungal sequences contained therein were 0.2% and 0.5% respectively. Among these sequences, only one could be 30 identified as a sequence specific to fungi. The others were either fungal or procaryotic sequences having homologies with vertebrate sequences or including repeat sequences which had not been masked during the electronic comparison.

In addition, the 5' ESTs were compared to 6093 Alu sequences and 1115 L1 sequences to mask 5' ESTs containing such repeat sequences from further consideration. 5' ESTs including THE and MER repeats, SSTR sequences or satellite, micro-satellite, or telomeric repeats were also eliminated from further consideration. On average, 11.5% of



The sequences of those 5' ESTs remaining after the elimination of undesirable sequences were compared with the sequences of known human mRNAs to determine the accuracy of the sequencing procedures described above.

### **EXAMPLE 19**

### Measurement of Sequencing Accuracy by Comparison to Known Sequences

To further determine the accuracy of the sequencing procedure described above, the sequences of 5' ESTs derived from known sequences were identified and compared to the known sequences. First, a FASTA analysis with overhangs shorter than 5 bp on both ends was conducted on the 5' ESTs to identify those matching an entry in the public human mRNA database. The 6655 5' ESTs which matched a known human mRNA were then realigned with their cognate mRNA and dynamic programming was used to include substitutions, insertions, and deletions in the list of 15 "errors" which would be recognized. Errors occurring in the last 10 bases of the 5' EST sequences were ignored to avoid the inclusion of spurious cloning sites in the analysis of sequencing accuracy.

This analysis revealed that the sequences incorporated in the NETGENE $^{ au_M}$  database had an accuracy of more than 99.5%.

To determine the efficiency with which the above selection procedures select cDNAs which include the 5' ends of their corresponding mRNAs, the following analysis was performed.

#### **EXAMPLE 20**

### Determination of Efficiency of 5' EST Selection

To determine the efficiency at which the above selection procedures isolated 5' ESTs which included sequences close to the 5' end of the mRNAs from which they were derived, the sequences of the ends of the 5' ESTs which were derived from the elongation factor 1 subunit lpha and ferritin heavy chain genes were compared to the known cDNA sequences for these genes. Since the transcription start sites for the elongation factor 1 subunit  $\alpha$  and ferritin heavy chain are well characterized, they may be used to determine the percentage of 5' ESTs derived from these genes which included the authentic transcription start sites.

For both genes, more than 95% of the cDNAs included sequences close to or upstream of the 5' end of the 30 corresponding mRNAs.

To extend the analysis of the reliability of the procedures for isolating 5' ESTs from ESTs in the NETGENETM database, a similar analysis was conducted using a database composed of human mRNA sequences extracted from GenBank database release 97 for comparison. For those 5' ESTs derived from mRNAs included in the GeneBank database, more than 85% had their 5' ends close to the 5' ends of the known sequence. As some of the mRNA



sequences available in the GenBank database are deduced from genomic sequences, a 5' end matching with these sequences will be counted as an internal match. Thus, the method used here underestimates the yield of ESTs including the authentic 5' ends of their corresponding mRNAs.

The EST libraries made above included multiple 5' ESTs derived from the same mRNA. The sequences of such 5' ESTs were compared to one another and the longest 5' ESTs for each mRNA were identified. Overlapping cDNAs were assembled into continuous sequences (contigs). The resulting continuous sequences were then compared to public databases to gauge their similarity to known sequences, as described in Example 21 below.

#### **EXAMPLE 21**

# Clustering of the 5' ESTs and Calculation of Novelty Indices for cDNA Libraries

For each sequenced EST library, the sequences were clustered by the 5' end. Each sequence in the library was compared to the others with BLASTN2 (direct strand, parameters S = 107). ESTs with High Scoring Segment Pairs (HSPs) at least 25 bp long, having 95% identical bases and beginning closer than 10 bp from each EST 5' end were grouped. The longest sequence found in the cluster was used as representative of the cluster. A global clustering between libraries was then performed leading to the definition of super-contigs.

To assess the yield of new sequences within the EST libraries, a novelty rate (NR) was defined as: NR = 100 X (Number of new unique sequences found in the library/Total number of sequences from the library). Typically, novelty rating range between 10% and 41% depending on the tissue from which the EST library was obtained. For most of the libraries, the random sequencing of 5' EST libraries was pursued until the novelty rate reached 20%.

Following characterization as described above, the collection of 5' ESTs in NETGENE<sup>TM</sup> was screened to identify those 5' ESTs bearing potential signal sequences as described in Example 22 below.

#### **EXAMPLE 22**

### Identification of Potential Signal Sequences in 5' ESTs

The 5' ESTs in the NETGENETM database were screened to identify those having an uninterrupted open reading frame (ORF) longer than 45 nucleotides beginning with an ATG codon and extending to the end of the EST.

25 Approximately half of the cDNA sequences in NETGENETM contained such an ORF. The ORFs of these 5' ESTs were searched to identify potential signal motifs using slight modifications of the procedures disclosed in Von Heijne, G. A New Method for Predicting Signal Sequence Cleavage Sites. Nucleic Acids Res. 14:4683-4690 (1986). Those 5' EST sequences encoding a 15 amino acid long stretch with a score of at least 3.5 in the Von Heijne signal peptide identification matrix were considered to possess a signal sequence. Those 5' ESTs which matched a known human MRNA or EST sequence and had a 5' end more than 20 nucleotides downstream of the known 5' end were excluded from further analysis. The remaining cDNAs having signal sequences therein were included in a database called SIGNALTAGTM.

To confirm the accuracy of the above method for identifying signal sequences, the analysis of Example 23 was performed.

#### **EXAMPLE 23**

### Confirmation of Accuracy of Identification of Potential Signal Sequences in 5' ESTs

The accuracy of the above procedure for identifying signal sequences encoding signal peptides was evaluated by applying the method to the 43 amino terminal amino acids of all human SwissProt proteins. The computed Von Heijne score for each protein was compared with the known characterization of the protein as being a secreted protein or a non-secreted protein. In this manner, the number of non-secreted proteins having a score higher than 3.5 (false positives) and the number of secreted proteins having a score lower than 3.5 (false negatives) could be calculated.

Using the results of the above analysis, the probability that a peptide encoded by the 5' region of the mRNA is in fact a genuine signal peptide based on its Von Heijne's score was calculated based on either the assumption that 10% of human proteins are secreted or the assumption that 20% of human proteins are secreted. The results of this analysis are shown in Figures 2 and 3.

Using the above method of identifying secretory proteins, 5' ESTs for human glucagon, gamma interferon induced monokine precursor, secreted cyclophilin-like protein, human pleiotropin, and human biotinidase precursor all of which are polypeptides which are known to be secreted, were obtained. Thus, the above method successfully identified those 5' ESTs which encode a signal peptide.

To confirm that the signal peptide encoded by the 5' ESTs actually functions as a signal peptide, the signal sequences from the 5' ESTs may be cloned into a vector designed for the identification of signal peptides. Some signal peptide identification vectors are designed to confer the ability to grow in selective medium on host cells which have a signal sequence operably inserted into the vector. For example, to confirm that a 5' EST encodes a genuine signal peptide, the signal sequence of the 5' EST may be inserted upstream and in frame with a non-secreted form of the yeast invertase gene in signal peptide selection vectors such as those described in U.S. Patent No. 5,536,637. Growth of host cells containing signal sequence selection vectors having the signal sequence from the 5' EST inserted therein confirms that the 5' EST encodes a genuine signal peptide.

Alternatively, the presence of a signal peptide may be confirmed by cloning the extended cDNAs obtained using
the ESTs into expression vectors such as pXT1 (as described below), or by constructing promoter-signal sequencereporter gene vectors which encode fusion proteins between the signal peptide and an assayable reporter protein. After
introduction of these vectors into a suitable host cell, such as COS cells or NIH 3T3 cells, the growth medium may be
harvested and analyzed for the presence of the secreted protein. The medium from these cells is compared to the
medium from cells containing vectors lacking the signal sequence or extended cDNA insert to identify vectors which
encode a functional signal peptide or an authentic secreted protein.

Those 5' ESTs which encoded a signal peptide, as determined by the method of Example 22 above, were further grouped into four categories based on their homology to known sequences. The categorization of the 5' ESTs is described in Example 24 below.

### **EXAMPLE 24**

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### Categorization of 5' ESTs Encoding a Signal Peptide

Those 5' ESTs having a sequence not matching any known vertebrate sequence nor any publicly available EST sequence were designated "new." Of the sequences in the SIGNALTAG™ database, 947 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those 5' ESTs having a sequence not matching any vertebrate sequence but matching a publicly known EST were designated "EST-ext", provided that the known EST sequence was extended by at least 40 nucleotides in the 5' direction. Of the sequences in the SIGNALTAG<sup>TM</sup> database, 150 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those ESTs not matching any vertebrate sequence but matching a publicly known EST without extending the known EST by at least 40 nucleotides in the 5' direction were designated "EST." Of the sequences in the SIGNALTAG<sup>TM</sup> database, 599 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those 5' ESTs matching a human mRNA sequence but extending the known sequence by at least 40 nucleotides in the 5' direction were designated "VERT-ext." Of the sequences in the SIGNALTAGTM database, 23 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category. Included in this category was a 5' EST which extended the known sequence of the human translocase mRNA by more than 200 bases in the 5' direction. A 5' EST which extended the sequence of a human tumor suppressor gene in the 5' direction was also identified.

Figure 4 shows the distribution of 5' ESTs in each category and the number of 5' ESTs in each category having a given minimum von Heijne's score.

Each of the 5' ESTs was categorized based on the tissue from which its corresponding mRNA was obtained, 20 as described below in Example 25.

### **EXAMPLE 25**

### **Categorization of Expression Patterns**

Figure 5 shows the tissues from which the mRNAs corresponding to the 5' ESTs in each of the above described categories were obtained.

In addition to categorizing the 5' ESTs by the tissue from which the cDNA library in which they were first identified was obtained, the spatial and temporal expression patterns of the mRNAs corresponding to the 5' ESTs, as well as their expression levels, may be determined as described in Example 26 below. Characterization of the spatial and temporal expression patterns and expression levels of these mRNAs is useful for constructing expression vectors capable of producing a desired level of gene product in a desired spatial or temporal manner, as will be discussed in more detail—30 below.

In addition, 5' ESTs whose corresponding mRNAs are associated with disease states may also be identified. For example, a particular disease may result from lack of expression, over expression, or under expression of an mRNA corresponding to a 5' EST. By comparing mRNA expression patterns and quantities in samples taken from healthy



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individuals with those from individuals suffering from a particular disease, 5' ESTs responsible for the disease may be identified.

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It will be appreciated that the results of the above characterization procedures for 5' ESTs also apply to extended cDNAs (obtainable as described below) which contain sequences adjacent to the 5' ESTs. It will also be appreciated that if it is desired to defer characterization until extended cDNAs have been obtained rather than characterizing the ESTs themselves, the above characterization procedures can be applied to characterize the extended cDNAs after their isolation.

#### **EXAMPLE 26**

# Evaluation of Expression Levels and Patterns of mRNAs Corresponding to 5' ESTs or Extended cDNAs

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Expression levels and patterns of mRNAs corresponding to 5' ESTs or extended cDNAs (obtainable as described below) may be analyzed by solution hybridization with long probes as described in International Patent Application No. WO 97/05277. Briefly, a 5' EST, extended cDNA, or fragment thereof corresponding to the gene encoding the mRNA to be characterized is inserted at a cloning site immediately downstream of a bacteriophage (T3, T7 or SP6) RNA polymerase promoter to produce antisense RNA. Preferably, the 5' EST or extended cDNA has 100 or more nucleotides. The plasmid is linearized and transcribed in the presence of ribonucleotides comprising modified ribonucleotides (i.e. biotin-UTP and DIG-UTP). An excess of this doubly labeled RNA is hybridized in solution with mRNA isolated from cells or tissues of interest. The hybridizations are performed under standard stringent conditions (40-50°C for 16 hours in an 80% formamide, 0.4 M NaCl buffer, pH 7-8). The unhybridized probe is removed by digestion with ribonucleases specific for single-stranded RNA (i.e. RNases CL3, T1, Phy M, U2 or A). The presence of the biotin-UTP modification enables capture of the hybrid on a microtitration plate coated with streptavidin. The presence of the DIG modification enables the hybrid to be detected and quantified by ELISA using an anti-DIG antibody coupled to alkaline phosphatase.

The 5' ESTs, extended cDNAs, or fragments thereof may also be tagged with nucleotide sequences for the

serial analysis of gene expression (SAGE) as disclosed in UK Patent Application No. 2 305 241 A. In this method,
cDNAs are prepared from a cell, tissue, organism or other source of nucleic acid for which it is desired to determine gene
expression patterns. The resulting cDNAs are separated into two pools. The cDNAs in each pool are cleaved with a first
restriction endonuclease, called an "anchoring enzyme," having a recognition site which is likely to be present at least
once in most cDNAs. The fragments which contain the 5' or 3' most region of the cleaved cDNA are isolated by binding
to a capture medium such as streptavidin coated beads. A first oligonucleotide linker having a first sequence for
hybridization of an amplification primer and an internal restriction site for a "tagging endonuclease" is ligated to the
digested cDNAs in the first pool. Digestion with the second endonuclease produces short "tag" fragments from the
cDNAs.



A second oligonucleotide having a second sequence for hybridization of an amplification primer and an internal restriction site is ligated to the digested cDNAs in the second pool. The cDNA fragments in the second pool are also digested with the "tagging endonuclease" to generate short "tag" fragments derived from the cDNAs in the second pool. The "tags" resulting from digestion of the first and second pools with the anchoring enzyme and the tagging 5 endonuclease are ligated to one another to produce "ditags." In some embodiments, the ditags are concatamerized to produce ligation products containing from 2 to 200 ditags. The tag sequences are then determined and compared to the sequences of the 5' ESTs or extended cDNAs to determine which 5' ESTs or extended cDNAs are expressed in the cell, tissue, organism, or other source of nucleic acids from which the tags were derived. In this way, the expression pattern of the 5' ESTs or extended cDNAs in the cell, tissue, organism, or other source of nucleic acids is obtained.

Quantitative analysis of gene expression may also be performed using arrays. As used herein, the term array means a one dimensional, two dimensional, or multidimensional arrangement of full length cDNAs (i.e. extended cDNAs which include the coding sequence for the signal peptide, the coding sequence for the mature protein, and a stop codon), extended cDNAs, 5' ESTs or fragments of the full length cDNAs, extended cDNAs, or 5' ESTs of sufficient length to permit specific detection of gene expression. Preferably, the fragments are at least 15 nucleotides in length. More preferably, the fragments are at least 100 nucleotides in length. More preferably, the fragments are more than 100 nucleotides in length. In some embodiments the fragments may be more than 500 nucleotides in length.

For example, quantitative analysis of gene expression may be performed with full length cDNAs, extended cDNAs, 5' ESTs, or fragments thereof in a complementary DNA microarray as described by Schena et al. (Science 270:467-470, 1995; Proc. Natl. Acad. Sci. U.S.A. 93:10614-10619, 1996). Full length cDNAs, extended cDNAs, 5' 20 ESTs or fragments thereof are amplified by PCR and arrayed from 96-well microtiter plates onto silylated microscope slides using high-speed robotics. Printed arrays are incubated in a humid chamber to allow rehydration of the array elements and rinsed, once in 0.2% SDS for 1 min, twice in water for 1 min and once for 5 min in sodium borohydride solution. The arrays are submerged in water for 2 min at 95°C, transferred into 0.2% SDS for 1 min, rinsed twice with water, air dried and stored in the dark at 25°C.

Cell or tissue mRNA is isolated or commercially obtained and probes are prepared by a single round of reverse transcription. Probes are hybridized to 1 cm² microarrays under a 14 x 14 mm glass coverslip for 6-12 hours at 60°C. Arrays are washed for 5 min at 25°C in low stringency wash buffer (1 x SSC/0.2% SDS), then for 10 min at room temperature in high stringency wash buffer (0.1 x SSC/0.2% SDS). Arrays are scanned in 0.1 x SSC using a fluorescence laser scanning device fitted with a custom filter set. Accurate differential expression measurements are 30 obtained by taking the average of the ratios of two independent hybridizations.

Quantitative analysis of the expression of genes may also be performed with full length cDNAs, extended cDNAs, 5' ESTs, or fragments thereof in complementary DNA arrays as described by Pietu et al. (Genome Research 6:492-503, 1996). The full length cDNAs, extended cDNAs, 5' ESTs or fragments thereof are PCR amplified and spotted on membranes. Then, mRNAs originating from various tissues or cells are labeled with radioactive nucleotides.

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After hybridization and washing in controlled conditions, the hybridized mRNAs are detected by phospho-imaging or autoradiography. Duplicate experiments are performed and a quantitative analysis of differentially expressed mRNAs is then performed.

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Alternatively, expression analysis of the 5' ESTs or extended cDNAs can be done through high density 5 nucleotide arrays as described by Lockhart et al. (Nature Biotechnology 14: 1675-1680, 1996) and Sosnowsky et al. (Proc. Natl. Acad. Sci. 94:1119-1123, 1997). Oligonucleotides of 15-50 nucleotides corresponding to sequences of the 5' ESTs or extended cDNAs are synthesized directly on the chip (Lockhart et al., supra) or synthesized and then addressed to the chip (Sosnowski et al., supra). Preferably, the oligonucleotides are about 20 nucleotides in length.

cDNA probes labeled with an appropriate compound, such as biotin, digoxigenin or fluorescent dye, are synthesized from the appropriate mRNA population and then randomly fragmented to an average size of 50 to 100 nucleotides. The said probes are then hybridized to the chip. After washing as described in Lockhart et al., supra and application of different electric fields (Sosnowsky et al., Proc. Natl. Acad. Sci. 94:1119-1123)., the dyes or labeling compounds are detected and quantified. Duplicate hybridizations are performed. Comparative analysis of the intensity of the signal originating from cDNA probes on the same target oligonucleotide in different cDNA samples indicates a 15 differential expression of the mRNA corresponding to the 5' EST or extended cDNA from which the oligonucleotide sequence has been designed.

### III. Use of 5' ESTs to Clone Extended cDNAs and to Clone the Corresponding Genomic DNAs

Once 5' ESTs which include the 5' end of the corresponding mRNAs have been selected using the procedures described above, they can be utilized to isolate extended cDNAs which contain sequences adjacent to the 5' ESTs. The 20 extended cDNAs may include the entire coding sequence of the protein encoded by the corresponding mRNA, including the authentic translation start site, the signal sequence, and the sequence encoding the mature protein remaining after cleavage of the signal peptide. Such extended cDNAs are referred to herein as "full length cDNAs." Alternatively, the extended cDNAs may include only the sequence encoding the mature protein remaining after cleavage of the signal peptide, or only the sequence encoding the signal peptide.

Example 27 below describes a general method for obtaining extended cDNAs. Example 28 below describes the cloning and sequencing of several extended cDNAs, including extended cDNAs which include the entire coding sequence and authentic 5' end of the corresponding mRNA for several secreted proteins.

The methods of Examples 27, 28, and 29 can also be used to obtain extended cDNAs which encode less than the entire coding sequence of the secreted proteins encoded by the genes corresponding to the 5' ESTs. In some 30 embodiments, the extended cDNAs isolated using these methods encode at least 10 amino acids of one of the proteins encoded by the sequences of SEQ ID NOs: 40-140 and 242-377. In further embodiments, the extended cDNAs encode at least 20 amino acids of the proteins encoded by the sequences of SEQ ID NOs: 40-140 and 242-377. In further embodiments, the extended cDNAs encode at least 30 amino amino acids of the sequences of SEQ ID NOs: 40-140 and



242-377. In a preferred embodiment, the extended cDNAs encode a full length protein sequence, which includes the protein coding sequences of SEO ID NOs: 40-140 and 242-377.

#### **EXAMPLE 27**

# General Method for Using 5' ESTs to Clone and Sequence Extended cDNAs

The following general method has been used to quickly and efficiently isolate extended cDNAs including sequence adjacent to the sequences of the 5' ESTs used to obtain them. This method may be applied to obtain extended cDNAs for any 5' EST in the NETGENE<sup>TM</sup> database, including those 5' ESTs encoding secreted proteins. The method is summarized in Figure 6.

### 1. Obtaining Extended cDNAs

### 10 a) First strand synthesis

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The method takes advantage of the known 5' sequence of the mRNA. A reverse transcription reaction is conducted on purified mRNA with a poly 14dT primer containing a 49 nucleotide sequence at its 5' end allowing the addition of a known sequence at the end of the cDNA which corresponds to the 3' end of the mRNA. For example, the primer may have the following sequence: 5'-ATC GTT GAG ACT CGT ACC AGC AGA GTC ACG AGA GAG ACT ACA CGG TAC TGG TTT TTT TTT TTT TTT TTVN -3' (SEQ ID NO:14). Those skilled in the art will appreciate that other sequences may also be added to the poly dT sequence and used to prime the first strand synthesis. Using this primer and a reverse transcriptase such as the Superscript II (Gibco BRL) or Rnase H Minus M-MLV (Promega) enzyme, a reverse transcript anchored at the 3' polyA site of the RNAs is generated.

After removal of the mRNA hybridized to the first cDNA strand by alkaline hydrolysis, the products of the alkaline hydrolysis and the residual poly dT primer are eliminated with an exclusion column such as an AcA34 (Biosepra) matrix as explained in Example 11.

### b) Second strand synthesis

A pair of nested primers on each end is designed based on the known 5' sequence from the 5' EST and the known 3' end added by the poly dT primer used in the first strand synthesis. Software used to design primers are either based on GC content and melting temperatures of oligonucleotides, such as OSP (Illier and Green, *PCR Meth. Appl.* 1:124-128, 1991), or based on the octamer frequency disparity method (Griffais et al., *Nucleic Acids Res.* 19: 3887-3891, 1991 such as PC-Rare (http://bioinformatics.weizmann.ac.il/software/PC-Rare/doc/manuel.html).

Preferably, the nested primers at the 5' end are separated from one another by four to nine bases. The 5' primer sequences may be selected to have melting temperatures and specificities suitable for use in PCR.

Preferably, the nested primers at the 3' end are separated from one another by four to nine bases. For example, the nested 3' primers may have the following sequences: (5'- CCA GCA GAG TCA CGA GAG AGA CTA CAC GG -3'(SEQ ID NO:15), and 5'- CAC GAG AGA GAC TAC ACG GTA CTG G -3' (SEQ ID NO:16). These primers were selected because they have melting temperatures and specificities compatible with their use in PCR. However, those skilled in the art will appreciate that other sequences may also be used as primers.

The first PCR run of 25 cycles is performed using the Advantage Tth Polymerase Mix (Clontech) and the outer-primer from each of the nested pairs. A second 20 cycle PCR using the same enzyme and the inner primer from each of the nested pairs is then performed on 1/2500 of the first PCR product. Thereafter, the primers and nucleotides are removed.

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### 5 2. Sequencing of Full Length Extended cDNAs or Fragments Thereof

Due to the lack of position constraints on the design of 5' nested primers compatible for PCR use using the OSP software, amplicons of two types are obtained. Preferably, the second 5' primer is located upstream of the translation initiation codon thus yielding a nested PCR product containing the whole coding sequence. Such a full length extended cDNA undergoes a direct cloning procedure as described in section a below. However, in some cases, the second 5' primer is located downstream of the translation initiation codon, thereby yielding a PCR product containing only part of the ORF. Such incomplete PCR products are submitted to a modified procedure described in section b below.

### a) Nested PCR products containing complete ORFs

When the resulting nested PCR product contains the complete coding sequence, as predicted from the 5'EST sequence, it is cloned in an appropriate vector such as pED6dpc2, as described in section 3.

### b) Nested PCR products containing incomplete ORFs

When the amplicon does not contain the complete coding sequence, intermediate steps are necessary to obtain both the complete coding sequence and a PCR product containing the full coding sequence. The complete coding sequence can be assembled from several partial sequences determined directly from different PCR products as described in the following section.

Once the full coding sequence has been completely determined, new primers compatible for PCR use are designed to obtain amplicons containing the whole coding region. However, in such cases, 3' primers compatible for PCR use are located inside the 3' UTR of the corresponding mRNA, thus yielding amplicons which lack part of this region, i.e. the polyA tract and sometimes the polyadenylation signal, as illustrated in figure 6. Such full length extended cDNAs are then cloned into an appropriate vector as described in section 3.

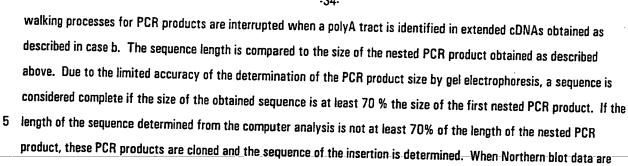
### c) Sequencing extended cDNAs

Sequencing of extended cDNAs is performed using a Die Terminator approach with the AmpliTaq DNA polymerase FS kit available from Perkin Elmer.

In order to sequence PCR fragments, primer walking is performed using software such as OSP to choose

30 primers and automated computer software such as ASMG (Sutton et al., *Genome Science Technol.* 1: 9-19, 1995) to construct contigs of walking sequences including the initial 5' tag using minimum overlaps of 32 nucleotides. Preferably, primer walking is performed until the sequences of full length cDNAs are obtained.

Completion of the sequencing of a given extended cDNA fragment is assessed as follows. Since sequences located after a polyA tract are difficult to determine precisely in the case of uncloned products, sequencing and primer



available, the size of the mRNA detected for a given PCR product is used to finally assess that the sequence is complete.

Sequence data of all extended cDNAs are then transferred to a proprietary database, where quality controls 10 and validation steps are carried out as described in example 15.

Sequences which do not fulfill the above criteria are discarded and will undergo a new isolation procedure.

### 3. Cloning of Full Length Extended cDNAs

The PCR product containing the full coding sequence is then cloned in an appropriate vector. For example, the extended cDNAs can be cloned into the expression vector pED6dpc2 (DiscoverEase, Genetics Institute, Cambridge, MA) as follows. The structure of pED6dpc2 is shown in Figure 7. pED6dpc2 vector DNA is prepared with blunt ends by 15 performing an EcoRI digestion followed by a fill in reaction. The blunt ended vector is dephosphorylated. After removal of PCR primers and ethanol precipitation, the PCR product containing the full coding sequence or the extended cDNA obtained as described above is phosphorylated with a kinase subsequently removed by phenol-Sevag extraction and precipitation. The double stranded extended cDNA is then ligated to the vector and the resulting expression plasmid introduced into appropriate host cells.

Since the PCR products obtained as described above are blunt ended molecules that can be cloned in either direction, the orientation of several clones for each PCR product is determined. Then, 4 to 10 clones are ordered in microtiter plates and subjected to a PCR reaction using a first primer located in the vector close to the cloning site and a second primer located in the portion of the extended cDNA corresponding to the 3' end of the mRNA. This second primer may be the antisense primer used in anchored PCR in the case of direct cloning (case a) or the antisense primer located 25 inside the 3'UTR in the case of indirect cloning (case b). Clones in which the start codon of the extended cDNA is operably linked to the promoter in the vector so as to permit expression of the protein encoded by the extended cDNA are conserved and sequenced. In addition to the ends of cDNA inserts, approximately 50 bp of vector DNA on each side of the cDNA insert are also sequenced.

The cloned PCR products are then entirely sequenced according to the aforementioned procedure. In this case, 30 contig assembly of long fragments is then performed on walking sequences that have already contigated for uncloned PCR products during primer walking. Sequencing of cloned amplicons is complete when the resulting contigs include the whole coding region as well as overlapping sequences with vector DNA on both ends.

### 4. Computer Analysis of Full Length Extended cDNA





Sequences of all full length extended cDNAs are then submitted to further analysis as described below and using the parameters found in Table II with the following modifications. For screening of miscellaneous subdivisions of Genbank, FASTA was used instead of BLASTN and 15 nucleotide of homology was the limit instead of 17. For Alu detection, BLASTN was used with the following parameters: S = 72; identity = 70%; and length = 40 nucleotides.

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Polyadenylation signal and polyA tail which were not search for the 5' ESTs were searched. For polyadenylation signal detection the signal (AATAAA) was searched with one permissible mismatch in the last ten nucleotides preceding the 5' end of the polyA. For the polyA, a stretch of 8 amino acids in the last 20 nucleotides of the sequence was searched with BLAST2N in the sense strand with the following parameters (W = 6, S = 10, E = 1000, and identity = 90%). Finally, patented sequences and ORF homologies were searched using, respectively, BLASTN and BLASTP on GenSEQ (Derwent's database of patented nucleotide sequences) and SWISSPROT for ORFs with the following parameters (W = 8).

(Derwent's database of patented nucleotide sequences) and SWISSPROT for ORFs with the following parameters (W = 8 and B = 10). Before examining the extended full length cDNAs for sequences of interest, extended cDNAs which are not of interest are searched as follows.

## a) Elimination of undesired sequences

Although 5'ESTs were checked to remove contaminant sequences as described in Example 18, a last verification was carried out to identify extended cDNAs sequences derived from undesired sequences such as vector RNAs, transfer RNAs, ribosomal rRNAs, mitochondrial RNAs, prokaryotic RNAs and fungal RNAs using the FASTA and BLASTN programs on both strands of extended cDNAs as described below.

To identify the extended cDNAs encoding vector RNAs, extended cDNAs are compared to the known sequences of vector RNA using the FASTA program. Sequences of extended cDNAs with more than 90% homology over stretches of 15 nucleotides are identified as vector RNA.

To identify the extended cDNAs encoding tRNAs, extended cDNA sequences were compared to the sequences of 1190 known tRNAs obtained from EMBL release 38, of which 100 were human. Sequences of extended cDNAs having more than 80% homology over 60 nucleotides using FASTA were identified as tRNA.

To identify the extended cDNAs encoding rRNAs, extended cDNA sequences were compared to the sequences of 2497 known rRNAs obtained from EMBL release 38, of which 73 were human. Sequences of extended cDNAs having more than 80% homology over stretches longer than 40 nucleotides using BLASTN were identified as rRNAs.

To identify the extended cDNAs encoding mtRNAs, extended cDNA sequences were compared to the sequences of the two known mitochondrial genomes for which the entire genomic sequences are available and all sequences transcribed from these mitochondrial genomes including tRNAs, rRNAs, and mRNAs for a total of 38 sequences. Sequences of extended cDNAs having more than 80% homology over stretches longer than 40 nucleotides using BLASTN were identified as mtRNAs.

Sequences which might have resulted from other exogenous contaminants were identified by comparing extended cDNA sequences to release 105 of Genbank bacterial and fungal divisions. Sequences of extended cDNAs





having more than 90% homology over 40 nucleotides using BLASTN were identified as exogenous prokaryotic or fungalcontaminants.

In addition, extended cDNAs were searched for different repeat sequences, including Alu sequences, L1 sequences, THE and MER repeats, SSTR sequences or satellite, micro-satellite, or telomeric repeats. Sequences of 5 extended cDNAs with more than 70% homology over 40 nucleotide stretches using BLASTN were identified as repeat sequences and masked in further identification procedures. In addition, clones showing extensive homology to repeats, i.e., matches of either more than 50 nucleotides if the homology was at least 75% or more than 40 nucleotides if the homology was at least 85% or more than 30 nucleotides if the homology was at least 90%, were flagged.

## b) Identification of structural features

Structural features, e.g. polyA tail and polyadenylation signal, of the sequences of full length extended cDNAs 10 are subsequently determined as follows.

A polyA tail is defined as a homopolymeric stretch of at least 11 A with at most one alternative base within it. The polyA tail search is restricted to the last 20 nt of the sequence and limited to stretches of 11 consecutive A's because sequencing reactions are often not readable after such a polyA stretch. Stretches with 100% homology over 6 15 nucleotides are identified as polyA tails.

To search for a polyadenylation signal, the polyA tail is clipped from the full-length sequence. The 50 bp preceding the polyA tail are searched for the canonic polyadenylation AAUAAA signal allowing one mismatch to account for possible sequencing errors and known variation in the canonical sequence of the polyadenylation signal.

## c) Identification of functional features

20 Functional features, e.g. ORFs and signal sequences, of the sequences of full length extended cDNAs were subsequently determined as follows.

The 3 upper strand frames of extended cDNAs are searched for ORFs defined as the maximum length fragments beginning with a translation initiation codon and ending with a stop codon. ORFs encoding at least 20 amino acids are preferred.

Each found ORF is then scanned for the presence of a signal peptide in the first 50 amino-acids or, where appropriate, within shorter regions down to 20 amino acids or less in the ORF, using the matrix method of von Heijne (Nuc. Acids Res. 14: 4683-4690 (1986)) and the modification described in Example 22.

# d) Homology to either nucleotidic or proteic sequences

Sequences of full length extended cDNAs are then compared to known sequences on a nucleotidic or proteic 30 basis.

Sequences of full length extended cDNAs are compared to the following known nucleic acid sequences: vertebrate sequences (Genbank), EST sequences (Genbank), patented sequences (Geneseqn) and recently identified sequences (Genbank daily releases) available at the time of filing for the priority documents. Full length cDNA sequences are also compared to the sequences of a private database (Genset internal sequences) in order to find sequences that

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have already been identified by applicants. Sequences of full length extended cDNAs with more than 90% homology over 30 nucleotides using either BLASTN or BLAST2N as indicated in Table III are identified as sequences that have already been described. Matching vertebrate sequences are subsequently examined using FASTA; full length extended cDNAs with more than 70% homology over 30 nucleotides are identified as sequences that have already been described.

ORFs encoded by full length extended cDNAs as defined in section c) are subsequently compared to known amino acid sequences found in Swissprot release CHP, PIR release PIR# and Genpept release GPEPT public databases using BLASTP with the parameter W = 8 and allowing a maximum of 10 matches. Sequences of full length extended cDNAs showing extensive homology to known protein sequences are recognized as already identified proteins.

In addition, the three-frame conceptual translation products of the top strand of full length extended cDNAs 10 are compared to publicly known amino acid sequences of Swissprot using BLASTX with the parameter E=0.001. Sequences of full length extended cDNAs with more than 70% homology over 30 amino acid stretches are detected as already identified proteins.

# 5. Selection of Cloned Full Length Sequences of the Present Invention

Cloned full length extended cDNA sequences that have already been characterized by the aforementioned 15 computer analysis are then submitted to an automatic procedure in order to preselect full length extended cDNAs containing sequences of interest.

### a) Automatic sequence preselection

All complete cloned full length extended cDNAs clipped for vector on both ends are considered. First, a negative selection is operated in order to eliminate unwanted cloned sequences resulting from either contaminants or 20 PCR artifacts as follows. Sequences matching contaminant sequences such as vector RNA, tRNA, mtRNA, rRNA sequences are discarded as well as those encoding ORF sequences exhibiting extensive homology to repeats as defined in section 4 a). Sequences obtained by direct cloning using nested primers on 5' and 3' tags (section 1, case a) but lacking polyA tail are discarded. Only ORFs containing a signal peptide and ending either before the polyA tail (case a) or before the end of the cloned 3'UTR (case b) are kept. Then, ORFs containing unlikely mature proteins such as mature 25 proteins which size is less than 20 amino acids or less than 25% of the immature protein size are eliminated.

In the selection of the OFR, priority was given to the ORF and the frame corresponding to the polypeptides described in SignalTag Patents (United States Patent Application Serial Nos: 08/905,223; 08/905,135; 08/905,051;  $08/905,144;\ 08/905,279;\ 08/904,468;\ 08/905,134;\ and\ 08/905,133).$  If the ORF was not found among the OFRs described in the SignalTag Patents, the ORF encoding the signal peptide with the highest score according to Von Heijne 30 method as defined in Example 22 was chosen. If the scores were identical, then the longest ORF was chosen.

Sequences of full length extended cDNA clones are then compared pairwise with BLAST after masking of the repeat sequences. Sequences containing at least 90% homology over 30 nucleotides are clustered in the same class. Each cluster is then subjected to a cluster analysis that detects sequences resulting from internal priming or from





alternative splicing, identical sequences or sequences with several frameshifts. This automatic analysis serves as a basis for manual selection of the sequences.

### b) Manual sequence selection

Manual selection is carried out using automatically generated reports for each sequenced full length extended cDNA clone. During this manual procedures, a selection is operated between clones belonging to the same class as follows. ORF sequences encoded by clones belonging to the same class are aligned and compared. If the homology between nucleotidic sequences of clones belonging to the same class is more than 90% over 30 nucleotide stretches or if the homology between amino acid sequences of clones belonging to the same class is more than 80% over 20 amino acid stretches, than the clones are considered as being identical. The chosen ORF is the best one according to the criteria mentioned below. If the nucleotide and amino acid homologies are less than 90% and 80% respectively, the clones are said to encode distinct proteins which can be both selected if they contain sequences of interest.

Selection of full length extended cDNA clones encoding sequences of interest is performed using the following criteria. Structural parameters (initial tag, polyadenylation site and signal) are first checked. Then, homologies with known nucleic acids and proteins are examined in order to determine whether the clone sequence match a known nucleic/proteic sequence and, in the latter case, its covering rate and the date at which the sequence became public. If there is no extensive match with sequences other than ESTs or genomic DNA, or if the clone sequence brings substantial new information, such as encoding a protein resulting from alternative slicing of an mRNA coding for an already known protein, the sequence is kept. Examples of such cloned full length extended cDNAs containing sequences of interest are described in Example 28. Sequences resulting from chimera or double inserts as assessed by homology to other sequences are discarded during this procedure.

### **EXAMPLE 28**

## Cloning and Sequencing of Extended cDNAs

The procedure described in Example 27 above was used to obtain the extended cDNAs of the present invention. Using this approach, the full length cDNA of SEQ ID NO:17 was obtained. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide MKKVLLLITAILAVAVG (SEQ ID NO: 18) having a von Heijne score of 8.2.

The full length cDNA of SEQ ID NO:19 was also obtained using this procedure. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide MWWFQQGLSFLPSALVIWTSA (SEQ ID NO:20) having a von Heijne score of 5.5.

Another full length cDNA obtained using the procedure described above has the sequence of SEQ ID NO:21.

This cDNA, falls into the "EST-ext" category described above and encodes the signal peptide

MVLTTLPSANSANSPVNMPTTGPNSLSYASSALSPCLT (SEQ ID NO:22) having a von Heijne score of 5.9.

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The above procedure was also used to obtain a full length cDNA having the sequence of SEQ ID NO:23. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide ILSTVTALTFAXA (SEQ ID NO:24) having a von Heijne score of 5.5.

The full length cDNA of SEQ ID NO:25 was also obtained using this procedure. This cDNA falls into the "new" category described above and encodes a signal peptide LVLTLCTLPLAVA (SEQ ID NO:26) having a von Heijne score of 10.1.

The full length cDNA of SEQ ID NO:27 was also obtained using this procedure. This cDNA falls into the "new" category described above and encodes a signal peptide LWLLFFLVTAIHA (SEQ ID NO:28) having a von Heijne score of 10.7.

The above procedures were also used to obtain the extended cDNAs of the present invention. 5' ESTs expressed in a variety of tissues were obtained as described above. The appended sequence listing provides the tissues from which the extended cDNAs were obtained. It will be appreciated that the extended cDNAs may also be expressed in tissues other than the tissue listed in the sequence listing.

5' ESTs obtained as described above were used to obtain extended cDNAs having the sequences of SEQ ID

NOs: 40-140 and 242-377. Table IV provides the sequence identification numbers of the extended cDNAs of the present invention, the locations of the full coding sequences in SEQ ID NOs: 40-140 and 242-377 (i.e. the nucleotides encoding both the signal peptide and the mature protein, listed under the heading FCS location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the signal peptides (listed under the heading SigPep Location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the mature proteins generated by cleavage of the signal peptides (listed under the heading Mature Polypeptide Location in Table IV), the locations in SEQ ID NOs: 40-140 and 242-377 of stop codons (listed under the heading Stop Codon Location in Table IV), the locations in SEQ ID NOs: 40-140 and 242-377 of polyA signals (listed under the heading Poly A Signal Location in Table IV) and the locations of polyA sites (listed under the heading Poly A Site Location in Table IV).

The polypeptides encoded by the extended cDNAs were screened for the presence of known structural or

functional motifs or for the presence of signatures, small amino acid sequences which are well conserved amongst the
members of a protein family. The conserved regions have been used to derive consensus patterns or matrices included in
the PROSITE data bank, in particular in the file prosite.dat (Release 13.0 of November 1995, located at
http://expasy.hcuge.ch/sprot/prosite.html. Prosite\_convert and prosite\_scan programs
(http://ulrec3.unil.ch/ftpserveur/prosite\_scan) were used to find signatures on the extended cDNAs.

For each pattern obtained with the prosite\_convert program from the prosite.dat file, the accuracy of the detection on a new protein sequence has been tested by evaluating the frequency of irrelevant hits on the population of human secreted proteins included in the data bank SWISSPROT. The ratio between the number of hits on shuffled proteins (with a window size of 20 amino acids) and the number of hits on native (unshuffled) proteins was used as an index. Every pattern for which the ration was greater than 20% (one hit on shuffled proteins for 5 hits on native



proteins) was skipped during the search with prosite\_scan. The program used to shuffle protein sequences (db\_shuffled) and the program used to determine the statistics for each pattern in the protein data banks (prosite\_statistics) are available on the ftp site http://ulrec3.unil.ch/ftpserveur/prosite\_scan.

Table V lists the sequence identification numbers of the polypeptides of SEQ ID NOs: 141-241 and 378-513, the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the full length polypeptide (second column), the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the signal peptides (third column), and the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the mature polypeptide created by cleaving the signal peptide from the full length polypeptide (fourth column).

The nucleotide sequences of the sequences of SEQ ID NOs: 40-140 and 242-377 and the amino acid sequences

10 encoded by SEQ ID NOs: 40-140 and 242-377 (i.e. amino acid sequences of SEQ ID NOs: 141-241 and 378-513) are

provided in the appended sequence listing. In some instances, the sequences are preliminary and may include some
incorrect or ambiguous sequences or amino acids. The sequences of SEQ ID NOs: 40-140 and 242-377 can readily be
screened for any errors therein and any sequence ambiguities can be resolved by resequencing a fragment containing
such errors or ambiguities on both strands. Nucleic acid fragments for resolving sequencing errors or ambiguities may be
obtained from the deposited clones or can be isolated using the techniques described herein. Resolution of any such
ambiguities or errors may be facilitated by using primers which hybridize to sequences located close to the ambiguous or
erroneous sequences. For example, the primers may hybridize to sequences within 50-75 bases of the ambiguity or
error. Upon resolution of an error or ambiguity, the corresponding corrections can be made in the protein sequences
encoded by the DNA containing the error or ambiguity. For example, in the sequences of the present invention, ambiguities
in the sequence of SEQ ID NO: 131 were resolved. The amino acid sequence of the protein encoded by a particular clone
can also be determined by expression of the clone in a suitable host cell, collecting the protein, and determining its
sequence.

For each amino acid sequence, Applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing. Some of the amino acid sequences may contain "Xaa" designators. These "Xaa" designators indicate either (1) a residue which cannot be identified because of nucleotide sequence ambiguity or (2) a stop codon in the determined sequence where Applicants believe one should not exist (if the sequence were determined more accurately).

Cells containing the extended cDNAs (SEQ ID NOs: 40-140 and 242-377) of the present invention in the vector pED6dpc2, are maintained in permanent deposit by the inventors at Genset, S.A., 24 Rue Royale, 75008 Paris, France.

Pools of cells containing the extended cDNAs (SEQ ID NOs: 40-140 and 242-377), from which cells containing a particular polynucleotide are obtainable, were deposited with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209 or the European Collection of Cell Cultures, Vaccine Research and Production Laboratory, Public Health Laboratory Service, Centre for Applied Microbiology and Research, Porton Down, Salisbury, Wiltshire SP4 OJG, United Kingdom. Each extended cDNA clone has been transfected into separate bacterial cells (E-

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coli) for this composite deposit. Table VI lists the deposit numbers of the clones containing the extended cDNAs of the present invention. Table VII provides the internal designation number assigned to each SEQ ID NO and indicates whether the sequence is a nucleic acid sequence or a protein sequence.

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Each extended cDNA can be removed from the pED6dpc2 vector in which it was deposited by performing a 5 Notl, Pstl double digestion to produce the appropriate fragment for each clone. The proteins encoded by the extended cDNAs may also be expressed from the promoter in pED6dpc2.

Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The design 10 of the oligonucleotide probe should preferably follow these parameters:

- (a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;
- (b) Preferably, the probe is designed to have a  $T_m$  of approx. 80°C (assuming 2 degrees for each A or T and 4 degrees for each G or C). However, probes having melting temperatures between 40 °C and 80 °C may also be used provided that specificity is not lost.

The oligonucleotide should preferably be labeled with (-[32P]ATP (specific activity 6000 Ci/mmole) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can aiso be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantified by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4X10<sup>6</sup> dpm/pmole.

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100  $\mu$ l of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100 ug/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing 25 ampicillin at 100 μg/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 30 175.3 g NaC1/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 pg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1X10<sup>6</sup> dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to

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1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

The plasmid DNA obtained using these procedures may then be manipulated using standard cloning techniques familiar to those skilled in the art. Alternatively, a PCR can be done with primers designed at both ends of the extended cDNA insertion. For example, a PCR reaction may be conducted using a primer having the sequence GGCCATACACTTGAGTGAC (SEQ ID NO:38) and a primer having the sequence ATATAGACAAACGCACACC (SEQ. ID. NO:39). The PCR product which corresponds to the extended cDNA can then be manipulated using standard cloning 10 techniques familiar to those skilled in the art.

In addition to PCR based methods for obtaining extended cDNAs, traditional hybridization based methods may also be employed. These methods may also be used to obtain the genomic DNAs which encode the mRNAs from which the 5' ESTs were derived, mRNAs corresponding to the extended cDNAs, or nucleic acids which are homologous to extended cDNAs or 5' ESTs. Example 29 below provides an example of such methods.

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### **EXAMPLE 29**

# Methods for Obtaining Extended cDNAs or Nucleic Acids Homologous to Extended cDNAs or 5' ESTs

A full length cDNA library can be made using the strategies described in Examples 13, 14, 15, and 16 above by replacing the random nonamer used in Example 14 with an oligo-dT primer. For instance, the oligonucleotide of SEQ ID 20 NO:14 may be used.

Alternatively, a cDNA library or genomic DNA library may be obtained from a commercial source or made using techniques familiar to those skilled in the art. The library includes cDNAs which are derived from the mRNA corresponding to a 5' EST or which have homology to an extended cDNA or 5' EST. The cDNA library or genomic DNA library is hybridized to a detectable probe comprising at least 10 consecutive nucleotides from the 5' EST or extended 25 cDNA using conventional techniques. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST or extended cDNA. More preferably, the probe comprises at least 20-30 consecutive nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises at least 30 nucleotides from the 5' EST or extended cDNA. In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST or extended cDNA.

Techniques for identifying cDNA clones in a cDNA library which hybridize to a given probe sequence are disclosed in Sambrook et al., Molecular Cloning: A Laboratory Manual 2d Ed., Cold Spring Harbor Laboratory Press, 1989. The same techniques may be used to isolate genomic DNAs.

Briefly, cDNA or genomic DNA clones which hybridize to the detectable probe are identified and isolated for further manipulation as follows. A probe comprising at least 10 consecutive nucleotides from the 5' EST or extended



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cDNA is labeled with a detectable label such as a radioisotope or a fluorescent molecule. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST or extended cDNA. More preferably, the probe comprises 20-30 consecutive nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises more than 30 nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST or extended cDNA.

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Techniques for labeling the probe are well known and include phosphorylation with polynucleotide kinase, nick translation, in vitro transcription, and non-radioactive techniques. The cDNAs or genomic DNAs in the library are transferred to a nitrocellulose or nylon filter and denatured. After incubation of the filter with a blocking solution, the filter is contacted with the labeled probe and incubated for a sufficient amount of time for the probe to hybridize to cDNAs or genomic DNAs containing a sequence capable of hybridizing to the probe.

By varying the stringency of the hybridization conditions used to identify extended cDNAs or genomic DNAs which hybridize to the detectable probe, extended cDNAS having different levels of homology to the probe can be identified and isolated. To identify extended cDNAs or genomic DNAs having a high degree of homology to the probe sequence, the melting temperature of the probe may be calculated using the following formulas:

For probes between 14 and 70 nucleotides in length the melting temperature (Tm) is calculated using the formula: Tm=81.5+16.6(log [Na+])+0.41(fraction G+C)-(600/N) where N is the length of the probe.

If the hybridization is carried out in a solution containing formamide, the melting temperature may be calculated using the equation Tm = 81.5 + 16.6(log [Na +]) + 0.41(fraction G + C)-(0.63% formamide)-(600/N) where N is the length of the probe.

Prehybridization may be carried out in 6X SSC, 5X Denhardt's reagent, 0.5% SDS, 100µg denatured fragmented salmon sperm DNA or 6X SSC, 5X Denhardt's reagent, 0.5% SDS, 100µg denatured fragmented salmon sperm DNA, 50% formamide. The formulas for SSC and Denhardt's solutions are listed in Sambrook et al., supra.

Hybridization is conducted by adding the detectable probe to the prehybridization solutions listed above. Where the probe comprises double stranded DNA, it is denatured before addition to the hybridization solution. The filter is contacted with the hybridization solution for a sufficient period of time to allow the probe to hybridize to extended cDNAs or genomic DNAs containing sequences complementary thereto or homologous thereto. For probes over 200 nucleotides in length, the hybridization may be carried out at 15-25°C below the Tm. For shorter probes, such as oligonucleotide probes, the hybridization may be conducted at 15-25°C below the Tm. Preferably, for hybridizations in 6X SSC, the hybridization is conducted at approximately 68°C. Preferably, for hybridizations in 50% formamide containing solutions, the hybridization is conducted at approximately 42°C.

All of the foregoing hybridizations would be considered to be under "stringent" conditions. Following hybridization, the filter is washed in 2X SSC, 0.1% SDS at room temperature for 15 minutes. The filter is then washed

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with 0.1X SSC, 0.5% SDS at room temperature for 30 minutes to 1 hour. Thereafter, the solution is washed at the hybridization temperature in 0.1X SSC, 0.5% SDS. A final wash is conducted in 0.1X SSC at room temperature.

Extended cDNAs, nucleic acids homologous to extended cDNAs or 5' ESTs, or genomic DNAs which have hybridized to the probe are identified by autoradiography or other conventional techniques.

The above procedure may be modified to identify extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs having decreasing levels of homology to the probe sequence. For example, to obtain extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs of decreasing homology to the detectable probe, less stringent conditions may be used. For example, the hybridization temperature may be decreased in increments of 5°C from 68°C to 42°C in a hybridization buffer having a Na+ concentration of approximately 1M. Following 10 hybridization, the filter may be washed with 2X SSC, 0.5% SDS at the temperature of hybridization. These conditions are considered to be "moderate" conditions above 50°C and "low" conditions below 50°C.

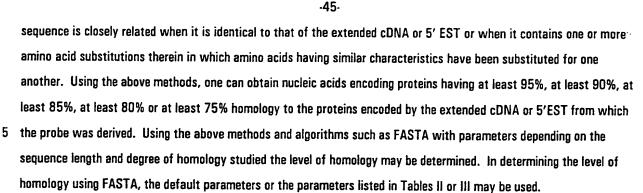
Alternatively, the hybridization may be carried out in buffers, such as 6X SSC, containing formamide at a temperature of 42°C. In this case, the concentration of formamide in the hybridization buffer may be reduced in 5%increments from 50% to 0% to identify clones having decreasing levels of homology to the probe. Following 15 hybridization, the filter may be washed with 6X SSC, 0.5% SDS at 50°C. These conditions are considered to be "moderate" conditions above 25% formamide and "low" conditions below 25% formamide.

Extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs which have hybridized to the probe are identified by autoradiography.

If it is desired to obtain nucleic acids homologous to extended cDNAs, such as allelic variants thereof or nucleic 20 acids encoding proteins related to the proteins encoded by the extended cDNAs, the level of homology between the hybridized nucleic acid and the extended cDNA or 5' EST used as the probe may readily be determined. To determine the level of homology between the hybridized nucleic acid and the extended cDNA or 5'EST from which the probe was derived, the nucleotide sequences of the hybridized nucleic acid and the extended cDNA or 5'EST from which the probe was derived are compared. For example, using the above methods, nucleic acids having at least 95% nucleic acid 25 homology to the extended cDNA or 5'EST from which the probe was derived may be obtained and identified. Similarly, by using progressively less stringent hybridization conditions one can obtain and identify nucleic acids having at least 90%, at least 85%, at least 80% or at least 75% homology to the extended cDNA or 5'EST from which the probe was derived. The level of homology between the hybridized nucleic acid and the extended cDNA or 5' EST used as the probe may be further determined using BLAST2N; parameters may be adapted depending on the sequence length and degree of 30 homology studied. In such comparisons, the default parameters or the parameters listed in Tables II and III may be used.

To determine whether a clone encodes a protein having a given amount of homology to the protein encoded by the extended cDNA or 5' EST, the amino acid sequence encoded by the extended cDNA or 5' EST is compared to the amino acid sequence encoded by the hybridizing nucleic acid. Homology is determined to exist when an amino acid sequence in the extended cDNA or 5' EST is closely related to an amino acid sequence in the hybridizing nucleic acid. A

-:3



Alternatively, extended cDNAs may be prepared by obtaining mRNA from the tissue, cell, or organism of interest using mRNA preparation procedures utilizing poly A selection procedures or other techniques known to those skilled in the art. A first primer capable of hybridizing to the poly A tail of the mRNA is hybridized to the mRNA and a reverse transcription reaction is performed to generate a first cDNA strand.

The first cDNA strand is hybridized to a second primer containing at least 10 consecutive nucleotides of the sequences of the 5' EST for which an extended cDNA is desired. Preferably, the primer comprises at least 12, 15, or 17 consecutive nucleotides from the sequences of the 5' EST. More preferably, the primer comprises 20-30 consecutive nucleotides from the sequences of the 5' EST. In some embodiments, the primer comprises more than 30 nucleotides from the sequences of the 5' EST. If it is desired to obtain extended cDNAs containing the full protein coding sequence, including the authentic translation initiation site, the second primer used contains sequences located upstream of the translation initiation site. The second primer is extended to generate a second cDNA strand complementary to the first cDNA strand. Alternatively, RTPCR may be performed as described above using primers from both ends of the cDNA to be obtained.

Extended cDNAs containing 5' fragments of the mRNA may be prepared by contacting an mRNA comprising the sequence of the 5' EST for which an extended cDNA is desired with a primer comprising at least 10 consecutive nucleotides of the sequences complementary to the 5' EST, hybridizing the primer to the mRNAs, and reverse transcribing the hybridized primer to make a first cDNA strand from the mRNAs. Preferably, the primer comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST. More preferably, the primer comprises 20-30 consecutive nucleotides from the 5' EST.

Thereafter, a second cDNA strand complementary to the first cDNA strand is synthesized. The second cDNA strand may be made by hybridizing a primer complementary to sequences in the first cDNA strand to the first cDNA strand and extending the primer to generate the second cDNA strand.

The double stranded extended cDNAs made using the methods described above are isolated and cloned. The extended cDNAs may be cloned into vectors such as plasmids or viral vectors capable of replicating in an appropriate host cell. For example, the host cell may be a bacterial, mammalian, avian, or insect cell.

Techniques for isolating mRNA, reverse transcribing a primer hybridized to mRNA to generate a first cDNA strand, extending a primer to make a second cDNA strand complementary to the first cDNA strand, isolating the double



stranded cDNA and cloning the double stranded cDNA are well known to those skilled in the art and are described in Current Protocols in Molecular Biology, John Wiley 503 Sons, Inc. 1997 and Sambrook et al. Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, 1989.

Alternatively, kits for obtaining full length cDNAs, such as the GeneTrapper (Cat. No. 10356-020, Gibco, BRL),

may be used for obtaining full length cDNAs or extended cDNAs. In this approach, full length or extended cDNAs are
prepared from mRNA and cloned into double stranded phagemids. The cDNA library in the double stranded phagemids is
then rendered single stranded by treatment with an endonuclease, such as the Gene II product of the phage F1, and
Exonuclease III as described in the manual accompanying the GeneTrapper kit. A biotinylated oligonucleotide comprising
the sequence of a 5' EST, or a fragment containing at least 10 nucleotides thereof, is hybridized to the single stranded
phagemids. Preferably, the fragment comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST. More
preferably, the fragment comprises 20-30 consecutive nucleotides from the 5' EST. In some procedures, the fragment
may comprise more than 30 consecutive nucleotides from the 5' EST. For example, the fragment may comprises at least
40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST.

Hybrids between the biotinylated oligonucleotide and phagemids having inserts containing the 5' EST sequence are isolated by incubating the hybrids with streptavidin coated paramagnetic beads and retrieving the beads with a magnet. Thereafter, the resulting phagemids containing the 5' EST sequence are released from the beads and converted into double stranded DNA using a primer specific for the 5' EST sequence. The resulting double stranded DNA is transformed into bacteria. Extended cDNAs containing the 5' EST sequence are identified by colony PCR or colony hybridization.

A plurality of extended cDNAs containing full length protein coding sequences or sequences encoding only the mature protein remaining after the signal peptide is cleaved may be provided as cDNA libraries for subsequent evaluation of the encoded proteins or use in diagnostic assays as described below.

# IV. Expression of Proteins Encoded by Extended cDNAs Isolated Using 5' ESTs

Extended cDNAs containing the full protein coding sequences of their corresponding mRNAs or portions

thereof, such as cDNAs encoding the mature protein, may be used to express the secreted proteins or portions thereof which they encode as described in Example 30 below. If desired, the extended cDNAs may contain the sequences encoding the signal peptide to facilitate secretion of the expressed protein. It will be appreciated that a plurality of extended cDNAs containing the full protein coding sequences or portions thereof may be simultaneously cloned into expression vectors to create an expression library for analysis of the encoded proteins as described below.

EXAMPLE 30

# Expression of the Proteins Encoded by Extended cDNAs or Portions Thereof

To express the proteins encoded by the extended cDNAs or portions thereof, nucleic acids containing the coding sequence for the proteins or portions thereof to be expressed are obtained as described in Examples 27-29 and cloned into a suitable expression vector. If desired, the nucleic acids may contain the sequences encoding the signal

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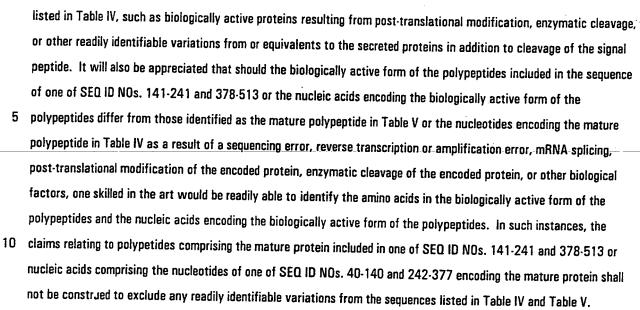
20

peptide to facilitate secretion of the expressed protein. For example, the nucleic acid may comprise the sequence of one of SEQ ID NOs: 40-140 and 242-377 listed in Table IV and in the accompanying sequence listing. Alternatively, the nucleic acid may comprise those nucleotides which make up the full coding sequence of one of the sequences of SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above.

It will be appreciated that should the extent of the full coding sequence (i.e. the sequence encoding the signal peptide and the mature protein resulting from cleavage of the signal peptide) differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the full coding sequences in the sequences of SEQ ID NOs. 40-140 and 242-377. 10 For example, the sequence of SEQ ID NO: 115 represents an alternatively spliced transcript of a previously identified mRNA.. Accordingly, the scope of any claims herein relating to nucleic acids containing the full coding sequence of one of SEQ ID NOs. 40-140 and 242-377 is not to be construed as excluding any readily identifiable variations from or equivalents to the full coding sequences listed in Table IV Similarly, should the extent of the full length polypeptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides 15 comprising the amino acid sequence of the full length polypeptides is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table V.

Alternatively, the nucleic acid used to express the protein or portion thereof may comprise those nucleotides which encode the mature protein (i.e. the protein created by cleaving the signal peptide off) encoded by one of the sequences of SEO ID NOs: 40-140 and 242-377 as defined in Table IV above.

It will be appreciated that should the extent of the sequence encoding the mature protein differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, posttranslational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the sequence encoding the mature protein in the sequences of SEQ ID NOs. 40-140 and 242-377. Accordingly, the scope of any claims herein relating to nucleic acids 25 containing the sequence encoding the mature protein encoded by one of SEQ ID Nos. 40-140 and 242-377 is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table IV. Thus, claims relating to nucleic acids containing the sequence encoding the mature protein encompass equivalents to the sequences listed in Table IV, such as sequences encoding biologically active proteins resulting from post-translational modification, enzymatic cleavage, or other readily identifiable variations from or equivalents to the secreted proteins in addition to cleavage of the signal peptide. Similarly, should the extent of the mature polypeptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides comprising the sequence of a mature protein included in the sequence of one of SEQ ID NOs. 141-241 and 378-513 is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table V. Thus, claims relating to polypeptides comprising the sequence of the mature protein encompass equivalents to the sequences



In some embodiments, the nucleic acid used to express the protein or portion thereof may comprise those nucleotides which encode the signal peptide encoded by one of the sequences of SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above.

It will be appreciated that should the extent of the sequence encoding the signal peptide differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the sequence encoding the signal peptide in the sequences of SEO ID NOs. 40-140 and 242-377. Accordingly, the scope of any claims herein relating to nucleic acids containing the sequence encoding the signal peptide encoded by one of SEO ID Nos. 40-140 and 242-377 is not to be construed as excluding any readily identifiable variations from the sequences listed in Table IV. Similarly, should the extent of the signal peptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides comprising the sequence of a signal peptide included in the sequence of one of SEO ID NOs. 141-241 and 378-513 is not to be construed as excluding any readily identifiable variations from the sequences listed in Table V.

Alternatively, the nucleic acid may encode a polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In some embodiments, the nucleic acid may encode a polypeptide comprising at least 15 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-30 513. In other embodiments, the nucleic acid may encode a polypeptide comprising at least 25 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In other embodiments, the nucleic acid may encode a polypeptide comprising at least 60, at least 75, at least 100 or more than 100 consecutive amino acids of one of the sequences of SEQ ID Nos: 141-241 and 378-513.

The nucleic acids inserted into the expression vectors may also contain sequences upstream of the sequences encoding the signal peptide, such as sequences which regulate expression levels or sequences which confer tissue specific expression.

The nucleic acid encoding the protein or polypeptide to be expressed is operably linked to a promoter in an expression vector using conventional cloning technology. The expression vector may be any of the mammalian, yeast, insect or bacterial expression systems known in the art. Commercially available vectors and expression systems are available from a variety of suppliers including Genetics Institute (Cambridge, MA), Stratagene (La Jolla, California), Promega (Madison, Wisconsin), and Invitrogen (San Diego, California). If desired, to enhance expression and facilitate proper protein folding, the codon context and codon pairing of the sequence may be optimized for the particular expression organism in which the expression vector is introduced, as explained by Hatfield, et al., U.S. Patent No. 5,082,767.

The following is provided as one exemplary method to express the proteins encoded by the extended cDNAs corresponding to the 5' ESTs or the nucleic acids described above. First, the methionine initiation codon for the gene and the poly A signal of the gene are identified. If the nucleic acid encoding the polypeptide to be expressed lacks a methionine to serve as the initiation site, an initiating methionine can be introduced next to the first codon of the nucleic acid using conventional techniques. Similarly, if the extended cDNA lacks a poly A signal, this sequence can be added to the construct by, for example, splicing out the Poly A signal from pSG5 (Stratagene) using Bgll and Sall restriction endonuclease enzymes and incorporating it into the mammalian expression vector pXT1 (Stratagene). pXT1 contains the LTRs and a portion of the gag gene from Moloney Murine Leukemia Virus. The position of the LTRs in the construct allow efficient stable transfection. The vector includes the Herpes Simplex Thymidine Kinase promoter and the selectable neomycin gene. The extended cDNA or portion thereof encoding the polypeptide to be expressed is obtained by PCR from the bacterial vector using oligonucleotide primers complementary to the extended cDNA or portion thereof and containing restriction endonuclease sequences for Pst I incorporated into the 5' primer and Bglll at the 5' end of the corresponding cDNA 3' primer, taking care to ensure that the extended cDNA is positioned in frame with the poly A signal. The purified fragment obtained from the resulting PCR reaction is digested with PstI, blunt ended with an exonuclease, digested with Bgl II, purified and ligated to pXT1, now containing a poly A signal and digested with BglII.

The ligated product is transfected into mouse NIH 3T3 cells using Lipofectin (Life Technologies, Inc., Grand Island, New York) under conditions outlined in the product specification. Positive transfectants are selected after growing the transfected cells in 600ug/ml G418 (Sigma, St. Louis, Missouri). Preferably the expressed protein is released into the culture medium, thereby facilitating purification.

Alternatively, the extended cDNAs may be cloned into pED6dpc2 as described above. The resulting pED6dpc2 constructs may be transfected into a suitable host cell, such as COS 1 cells. Methotrexate resistant cells are selected and expanded. Preferably, the protein expressed from the extended cDNA is released into the culture medium thereby facilitating purification.



Proteins in the culture medium are separated by gel electrophoresis. If desired, the proteins may be ammonium sulfate precipitated or separated based on size or charge prior to electrophoresis.

As a control, the expression vector lacking a cDNA insert is introduced into host cells or organisms and the proteins in the medium are harvested. The secreted proteins present in the medium are detected using techniques such as Coomassie or silver staining or using antibodies against the protein encoded by the extended cDNA. Coomassie and silver staining techniques are familiar to those skilled in the art.

Antibodies capable of specifically recognizing the protein of interest may be generated using synthetic 15-mer peptides having a sequence encoded by the appropriate 5' EST, extended cDNA, or portion thereof. The synthetic peptides are injected into mice to generate antibody to the polypeptide encoded by the 5' EST, extended cDNA, or portion thereof.

Secreted proteins from the host cells or organisms containing an expression vector which contains the extended cDNA derived from a 5' EST or a portion thereof are compared to those from the control cells or organism. The presence of a band in the medium from the cells containing the expression vector which is absent in the medium from the control cells indicates that the extended cDNA encodes a secreted protein. Generally, the band corresponding to the protein encoded by the extended cDNA will have a mobility near that expected based on the number of amino acids in the open reading frame of the extended cDNA. However, the band may have a mobility different than that expected as a result of modifications such as glycosylation, ubiquitination, or enzymatic cleavage.

Alternatively, if the protein expressed from the above expression vectors does not contain sequences directing its secretion, the proteins expressed from host cells containing an expression vector containing an insert encoding a secreted protein or portion thereof can be compared to the proteins expressed in host cells containing the expression vector without an insert. The presence of a band in samples from cells containing the expression vector without an insert indicates that the desired protein or portion thereof is being expressed. Generally, the band will have the mobility expected for the secreted protein or portion thereof. However, the band may have a mobility different than that expected as a result of modifications such as glycosylation, ubiquitination, or enzymatic cleavage.

The protein encoded by the extended cDNA may be purified using standard immunochromatography techniques. In such procedures, a solution containing the secreted protein, such as the culture medium or a cell extract, is applied to a column having antibodies against the secreted protein attached to the chromatography matrix. The secreted protein is allowed to bind the immunochromatography column. Thereafter, the column is washed to remove non-specifically bound proteins. The specifically bound secreted protein is then released from the column and recovered using standard techniques.

If antibody production is not possible, the extended cDNA sequence or portion thereof may be incorporated into expression vectors designed for use in purification schemes employing chimeric polypeptides. In such strategies the coding sequence of the extended cDNA or portion thereof is inserted in frame with the gene encoding the other half of

the chimera. The other half of the chimera may be β-globin or a nickel binding polypeptide encoding sequence. A chromatography matrix having antibody to β-globin or nickel attached thereto is then used to purify the chimeric protein. Protease cleavage sites may be engineered between the β-globin gene or the nickel binding polypeptide and the extended cDNA or portion thereof. Thus, the two polypeptides of the chimera may be separated from one another by protease digestion.

One useful expression vector for generating β-globin chimerics is pSG5 (Stratagene), which encodes rabbit β-globin. Intron II of the rabbit β-globin gene facilitates splicing of the expressed transcript, and the polyadenylation signal incorporated into the construct increases the level of expression. These techniques as described are well known to those skilled in the art of molecular biology. Standard methods are published in methods texts such as Davis et al.,

(Basic Methods in Molecular Biology, L.G. Davis, M.D. Dibner, and J.F. Battey, ed., Elsevier Press, NY, 1986) and many of the methods are available from Stratagene, Life Technologies, Inc., or Promega. Polypeptide may additionally be produced from the construct using in vitro translation systems such as the In vitro Express<sup>TM</sup> Translation Kit (Stratagene).

Following expression and purification of the secreted proteins encoded by the 5' ESTs, extended cDNAs, or fragments thereof, the purified proteins may be tested for the ability to bind to the surface of various cell types as described in Example 31 below. It will be appreciated that a plurality of proteins expressed from these cDNAs may be included in a panel of proteins to be simultaneously evaluated for the activities specifically described below, as well as other biological roles for which assays for determining activity are available.

#### **EXAMPLE 31**

Analysis of Secreted Proteins to Determine Whether they Bind to the Cell Surface

The proteins encoded by the 5' ESTs, extended cDNAs, or fragments thereof are cloned into expression vectors such as those described in Example 30. The proteins are purified by size, charge, immunochromatography or other techniques familiar to those skilled in the art. Following purification, the proteins are labeled using techniques known to those skilled in the art. The labeled proteins are incubated with cells or cell lines derived from a variety of organs or tissues to allow the proteins to bind to any receptor present on the cell surface. Following the incubation, the cells are washed to remove non-specifically bound protein. The labeled proteins are detected by autoradiography. Alternatively, unlabeled proteins may be incubated with the cells and detected with antibodies having a detectable label, such as a fluorescent molecule, attached thereto.

Specificity of cell surface binding may be analyzed by conducting a competition analysis in which various amounts of unlabeled protein are incubated along with the labeled protein. The amount of labeled protein bound to the cell surface decreases as the amount of competitive unlabeled protein increases. As a control, various amounts of an unlabeled protein unrelated to the labeled protein is included in some binding reactions. The amount of labeled protein bound to the cell surface does not decrease in binding reactions containing increasing amounts of unrelated unlabeled protein, indicating that the protein encoded by the cDNA binds specifically to the cell surface.





As discussed above, secreted proteins have been shown to have a number of important physiological effects and, consequently, represent a valuable therapeutic resource. The secreted proteins encoded by the extended cDNAs or portions thereof made according to Examples 27-29 may be evaluated to determine their physiological activities as described below.

## 5 EXAMPLE 32

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Cytokine, Cell Proliferation or Cell **Differentiation Activity** 

As discussed above, secreted proteins may act as cytokines or may affect cellular proliferation or differentiation. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or 10 more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B5, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7c and CMK. The proteins encoded by the above extended cDNAs or portions thereof may be evaluated for their ability to regulate T cell or thymocyte proliferation 15 in assays such as those described above or in the following references: Current Protocols in Immunology, Ed. by J.E. Coligan et al., Greene Publishing Associates and Wiley-Interscience; Takai et al. J. Immunol. 137:3494-3500, 1986. Bertagnolli et al. J. Immunol. 145:1706-1712, 1990. Bertagnolli et al., Cellular Immunology 133:327-341, 1991. Bertagnolli, et al. J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152:1756-1761, 1994.

In addition, numerous assays for cytokine production and/or the proliferation of spleen cells, lymph node cells 20 and thymocytes are known. These include the techniques disclosed in Current Protocols in Immunology. J.E. Coligan et al. Eds., Vol 1 pp. 3.12.1-3.12.14 John Wiley and Sons, Toronto. 1994; and Schreiber, R.D. Current Protocols in Immunology., supra Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

The proteins encoded by the cDNAs may also be assayed for the ability to regulate the proliferation and differentiation of hematopoietic or lymphopoietic cells. Many assays for such activity are familiar to those skilled in the 25 art, including the assays in the following references: Bottomly, K., Davis, L.S. and Lipsky, P.E., Measurement of Human and Murine Interleukin 2 and Interleukin 4, Current Protocols in Immunology., J.E. Coligan et al. Eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 36:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Nordan, R., Measurement of Mouse and Human Interleukin 6 Current Protocols in Immunology. J.E. Coligan et al. Eds. Vol 1 pp. 6.6.1-6.6.5, 30 John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Bennett, F., Giannotti, J., Clark, S.C. and Turner, K.J., Measurement of Human Interleukin 11 Current Protocols in Immunology. J.E. Coligan et al. Eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J., Measurement of Mouse and Human Interleukin 9 Current Protocols in Immunology. J.E. Coligan et al., Eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.



The proteins encoded by the cDNAs may also be assayed for their ability to regulate T-cell responses to antigens. Many assays for such activity are familiar to those skilled in the art, including the assays described in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte Function), Chapter 6 (Cytokines and Their Cellular Receptors) and Chapter 7, (Immunologic Studies in Humans) in Current Protocols in Immunology, J.E. Coligan 5 et al. Eds. Greene Publishing Associates and Wiley-Interscience; Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Those proteins which exhibit cytokine, cell proliferation, or cell differentiation activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which induction of cell proliferation or differentiation is 10 beneficial. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

#### **EXAMPLE 33**

# Assaying the Proteins Expressed from Extended cDNAs or Portions

# Thereof for Activity as Immune System Regulators

The proteins encoded by the cDNAs may also be evaluated for their effects as immune regulators. For example, the proteins may be evaluated for their activity to influence thymocyte or splenocyte cytotoxicity. Numerous assays for such activity are familiar to those skilled in the art including the assays described in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte Function 3.1-3.19) and Chapter 7 (Immunologic studies in Humans) in 20 Current Protocols in Immunology, J.E. Coligan et al. Eds, Greene Publishing Associates and Wiley-Interscience; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 25 137:3494-3500, 1986; Bowman et al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

The proteins encoded by the cDNAs may also be evaluated for their effects on T-cell dependent immunoglobulin responses and isotype switching. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Maliszewski, J. Immunol. 144:3028-3033, 1990; Mond, J.J. and 30 Brunswick, M Assays for B Cell Function: In vitro Antibody Production, Vol 1 pp. 3.8.1-3.8.16 in Current Protocols in Immunology. J.E. Coligan et al Eds., John Wiley and Sons, Toronto. 1994.

The proteins encoded by the cDNAs may also be evaluated for their effect on immune effector cells, including their effect on Th1 cells and cytotoxic lymphocytes. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte



Function 3.1-3.19) and Chapter 7 (Immunologic Studies in Humans) in **Current Protocols in Immunology**, J.E. Coligan et al. Eds., Greene Publishing Associates and Wiley-Interscience; Takai et al., **J. Immunol.** 137:3494-3500, 1986; Takai et al.; **J. Immunol.** 140:508-512, 1988; Bertagnolli et al., **J. Immunol.** 149:3778-3783, 1992.

The proteins encoded by the cDNAs may also be evaluated for their effect on dendritic cell mediated activation of naive T-cells. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

The proteins encoded by the cDNAs may also be evaluated for their influence on the lifetime of lymphocytes.

Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Those proteins which exhibit activity as immune system regulators activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of immune activity is beneficial. For example, the protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases caused by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis,

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myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to regulate immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T-cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. 10 Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte 15 antigen functions (such as, for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an 25 immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed 30 using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4lg fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models



of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function in vivo on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which 5 promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead 10 to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/pr/pr mice or NZB hybrid mice, murine autoimmuno collagen arthritis, diabetes mellitus in OD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory 20 form of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to T cells in vivo, thereby activating the T cells.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (e.g., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be 30 transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acids encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β<sub>2</sub> macroglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class II or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain,can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

### **EXAMPLE 34**

# Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Hematopoiesis Regulating Activity

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their hematopoiesis regulating activity. For example, the effect of the proteins on embryonic stem cell differentiation may be evaluated. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their influence on the lifetime of stem cells and stem cell differentiation. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Freshney, M.G. Methylcellulose Colony Forming Assays, in Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds. pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; McNiece, I.K. and Briddell, R.A. Primitive Hematopoietic Colony Forming Cells with High Proliferative Potential, in Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Ploemacher, R.E. Cobblestone Area Forming Cell Assay, In Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds. pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Spooncer, E., Dexter, M. and Allen, T. Long Term Bone Marrow Cultures in the Presence of Stromal Cells, in Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds.



pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; and Sutherland, H.J. Long Term Culture Initiating Cell Assay, in Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds. pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Those proteins which exhibit hematopoiesis regulatory activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of hematopoeisis is beneficial. For example, a protein of the present 5 invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell linesindicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid 10 cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelosuppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem 15 cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantion, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or 20 genetically manipulated for gene therapy. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

# **EXAMPLE 35**

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Regulation of Tissue Growth

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their effect on tissue growth. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in International Patent Publication No. W095/16035, International Patent Publication No. W095/05846 and International Patent Publication No. W091/07491.

Assays for wound healing activity include, without limitation, those described in: Winter, <u>Epidermal Wound</u>

30 <u>Healing</u>, pps. 71-112 (Maibach, H1 and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Those proteins which are involved in the regulation of tissue growth may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of tissue growth is beneficial. For example, a protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or

nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

15 Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to 20 tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate 25 growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e., for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as





Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium) muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to generate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokinc damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

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### **EXAMPLE 36**

# Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Regulation of Reproductive Hormones or Cell Movement

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their ability to regulate reproductive hormones, such as follicle stimulating hormone. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986. Chapter 6.12 (Measurement of Alpha and Beta Chemokines) Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Intersciece; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller 30 et al. Eur. J. Immunol. 25:1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153:1762-1768, 1994.

Those proteins which exhibit activity as reproductive hormones or regulators of cell movement may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of reproductive hormones or cell movement are beneficial. For example, a protein of the present invention may also exhibit activin- or inhibin-related

activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins are characterized by their ability to stimulate the release of folic stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals.

Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-B group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

### **EXAMPLE 36A**

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# Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Chemotactic/Chemokinetic Activity

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for chemotactic/chemokinetic activity. For example, a protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, cosinophils, epithelial and/or endothelial cells. Chemotactic and chmokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhension of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12,





Measurement of alpha and beta Chemokincs 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Mueller et al Eur. J. Immunol. 25:1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol, 153:1762-1768, 1994.

### **EXAMPLE 37**

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# Assaying the Proteins Expressed from Extended cDNAs or

# Portions Thereof for Regulation of Blood Clotting

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their effects on blood clotting. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res.

45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Those proteins which are involved in the regulation of blood clotting may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of blood clotting is beneficial. For example, a protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulations disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke). Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

### **EXAMPLE 38**

# Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Involvement in Receptor/Ligand Interactions

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for their involvement in receptor/ligand interactions. Numerous assays for such involvement are familiar to those skilled in the art, including the assays disclosed in the following references: Chapter 7.28 (Measurement of Cellular Adhesion under Static Conditions 7.28.1-7.28.22) in Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Interscience; Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160, 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995; Gyuris et al., Cell 75:791-803, 1993.

For example, the proteins of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion





molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune respones). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

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### **EXAMPLE 38A**

# Assaying the Proteins Expressed from Extended cDNAs or Portions

# Thereof for Anti-Inflammatory Activity

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusioninury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

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### **EXAMPLE 38B**

# Assaying the Proteins Expressed from Extended cDNAs or

# Portions Thereof for Tumor Inhibition Activity

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for tumor inhibition activity. In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, climinating or inhibiting factors, agents or cell types which promote tumor growth.

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or



circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or climination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

### **EXAMPLE 39**

# Identification of Proteins which Interact with Polypeptides Encoded by Extended cDNAs

Proteins which interact with the polypeptides encoded by extended cDNAs or portions thereof, such as

receptor proteins, may be identified using two hybrid systems such as the Matchmaker Two Hybrid System 2 (Catalog No. K1604-1, Clontech). As described in the manual accompanying the Matchmaker Two Hybrid System 2 (Catalog No. K1604-1, Clontech), the extended cDNAs or portions thereof, are inserted into an expression vector such that they are in frame with DNA encoding the DNA binding domain of the yeast transcriptional activator GAL4. cDNAs in a cDNA library which encode proteins which might interact with the polypeptides encoded by the extended cDNAs or portions thereof are inserted into a second expression vector such that they are in frame with DNA encoding the activation domain of GAL4. The two expression plasmids are transformed into yeast and the yeast are plated on selection medium which selects for expression of selectable markers on each of the expression vectors as well as GAL4 dependent expression of the HIS3 gene. Transformants capable of growing on medium lacking histidine are screened for GAL4 dependent lacZ expression. Those cells which are positive in both the histidine selection and the lacZ assay contain plasmids encoding proteins which interact with the polypeptide encoded by the extended cDNAs or portions thereof.

Alternatively, the system described in Lustig et al., Methods in Enzymology 283: 83-99 (1997) may be used for identifying molecules which interact with the polypeptides encoded by extended cDNAs. In such systems, in vitro transcription reactions are performed on a pool of vectors containing extended cDNA inserts cloned downstream of a promoter which drives in vitro transcription. The resulting pools of mRNAs are introduced into Xenopus laevis oocytes.

30 The oocytes are then assayed for a desired acitivity.

Alternatively, the pooled *in vitro* transcription products produced as described above may be translated *in vitro*. The pooled *in vitro* translation products can be assayed for a desired activity or for interaction with a known polypeptide.

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Proteins or other molecules interacting with polypeptides encoded by extended cDNAs can be found by a variety of additional techniques. In one method, affinity columns containing the polypeptide encoded by the extended cDNA or a portion thereof can be constructed. In some versions, of this method the affinity column contains chimeric proteins in which the protein encoded by the extended cDNA or a portion thereof is fused to glutathione S-transferase. 5 A mixture of cellular proteins or pool of expressed proteins as described above and is applied to the affinity column. Proteins interacting with the polypeptide attached to the column can then be isolated and analyzed on 2-D electrophoresis gel as described in Ramunsen et al. Electrophoresis, 18, 588-598 (1997). Alternatively, the proteins retained on the affinity column can be purified by electrophoresis based methods and sequenced. The same method can be used to isolate antibodies, to screen phage display products, or to screen phage display human antibodies.

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Proteins interacting with polypeptides encoded by extended cDNAs or portions thereof can also be screened by using an Optical Biosensor as described in Edwards & Leatherbarrow, Analytical Biochemistry, 246, 1-6 (1997). The main advantage of the method is that it allows the determination of the association rate between the protein and other interacting molecules. Thus, it is possible to specifically select interacting molecules with a high or low association rate. Typically a target molecule is linked to the sensor surface (through a carboxymethl dextran matrix) and a sample of test 15 molecules is placed in contact with the target molecules. The binding of a test molecule to the target molecule causes a change in the refractive index and/ or thickness. This change is detected by the Biosensor provided it occurs in the evanescent field (which extend a few hundred manometers from the sensor surface). In these screening assays, the target molecule can be one of the polypeptides encoded by extended cDNAs or a portion thereof and the test sample can be a collection of proteins extracted from tissues or cells, a pool of expressed proteins, combinatorial peptide and/ or 20 chemical libraries, or phage displayed peptides. The tissues or cells from which the test proteins are extracted can originate from any species.

In other methods, a target protein is immobilized and the test population is a collection of unique polypeptides encoded by the extended cDNAs or portions thereof.

To study the interaction of the proteins encoded by the extended cDNAs or portions thereof with drugs, the 25 microdialysis coupled to HPLC method described by Wang et al., Chromatographia, 44, 205-208(1997) or the affinity capillary electrophoresis method described by Busch et al., J. Chromatogr. 777:311-328 (1997), the disclosures of which are incorporated herein by referenc can be used.

The system described in U.S. Patent No. 5,654,150 may also be used to identify molecules which interact with the polypeptides encoded by the extended cDNAs. In this system, pools of extended cDNAs are transcribed and 30 translated in vitro and the reaction products are assayed for interaction with a known polypeptide or antibody.

It will be appreciated by those skilled in the art that the proteins expressed from the extended cDNAs or portions may be assayed for numerous activities in addition to those specifically enumerated above. For example, the expressed proteins may be evaluated for applications involving control and regulation of inflammation, tumor



proliferation or metastasis, infection, or other clinical conditions. In addition, the proteins expressed from the extended cDNAs or portions thereof may be useful as nutritional agents or cosmetic agents.

The proteins expressed from the extended cDNAs or portions thereof may be used to generate antibodies capable of specifically binding to the expressed protein or fragments thereof as described in Example 40 below. The antibodies may capable of binding a full length protein encoded by one of the sequences of SEQ ID NOs. 40-140 and 242-377, a mature protein encoded by one of the sequences of SEQ ID NOs. 40-140 and 242-377, or a signal peptide encoded by one of the sequences of SEQ ID Nos. 40-140 and 242-377. Alternatively, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 10 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513. In some embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 15 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513. In other embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 25 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513. In further embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 40 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513.

### **EXAMPLE 40**

# Production of an Antibody to a Human Protein

Substantially pure protein or polypeptide is isolated from the transfected or transformed cells as described in Example 30. The concentration of protein in the final preparation is adjusted, for example, by concentration on an Amicon filter device, to the level of a few micrograms/ml. Monoclonal or polyclonal antibody to the protein can then be prepared as follows:

# A. Monoclonal Antibody Production by Hybridoma Fusion

Monoclonal antibody to epitopes of any of the peptides identified and isolated as described can be prepared from murine hybridomas according to the classical method of Kohler, G. and Milstein, C., Nature 256:495 (1975) or derivative methods thereof. Briefly, a mouse is repetitively inoculated with a few micrograms of the selected protein or peptides derived therefrom over a period of a few weeks. The mouse is then sacrificed, and the antibody producing cells of the spleen isolated. The spleen cells are fused by means of polyethylene glycol with mouse myeloma cells, and the excess unfused cells destroyed by growth of the system on selective media comprising aminopterin (HAT media). The successfully fused cells are diluted and aliquots of the dilution placed in wells of a microtiter plate where growth of the successfully fused cells are diluted and aliquots of the dilution placed in wells of a microtiter plate where growth of the culture is continued. Antibody-producing clones are identified by detection of antibody in the supernatant fluid of the wells by immunoassay procedures, such as Elisa, as originally described by Engvall, E., Meth. Enzymol. 70:419 (1980), and derivative methods thereof. Selected positive clones can be expanded and their monoclonal antibody product harvested for use. Detailed procedures for monoclonal antibody production are described in Davis, L. et al. Basic Methods in Molecular Biology Elsevier, New York. Section 21-2.



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#### B. **Polyclonal Antibody Production by Immunization**

Polyclonal antiserum containing antibodies to heterogenous epitopes of a single protein can be prepared by immunizing suitable animals with the expressed protein or peptides derived therefrom described above, which can be unmodified or modified to enhance immunogenicity. Effective polyclonal antibody production is affected by many factors 5 related both to the antigen and the host species. For example, small molecules tend to be less immunogenic than others and may require the use of carriers and adjuvant. Also, host animals vary in response to site of inoculations and dose, with both inadequate or excessive doses of antigen resulting in low titer antisera. Small doses (ng level) of antigen administered at multiple intradermal sites appears to be most reliable. An effective immunization protocol for rabbits can be found in Vaitukaitis, J. et al. J. Clin. Endocrinol. Metab. 33:988-991 (1971).

Booster injections can be given at regular intervals, and antiserum harvested when antibody titer thereof, as determined semi-quantitatively, for example, by double immunodiffusion in agar against known concentrations of the antigen, begins to fall. See, for example, Ouchterlony, O. et al., Chap. 19 in: Handbook of Experimental Immunology D. Wier (ed) Blackwell (1973). Plateau concentration of antibody is usually in the range of 0.1 to 0.2 mg/ml of serum (about 12  $\mu$ M). Affinity of the antisera for the antigen is determined by preparing competitive binding curves, as described, for example, by Fisher, D., Chap. 42 in: Manual of Clinical Immunology, 2d Ed. (Rose and Friedman, Eds.) Amer. Soc. For Microbiol., Washington, D.C. (1980).

Antibody preparations prepared according to either protocol are useful in quantitative immunoassays which determine concentrations of antigen-bearing substances in biological samples; they are also used semi-quantitatively or qualitatively to identify the presence of antigen in a biological sample. The antibodies may also be used in therapeutic 20 compositions for killing cells expressing the protein or reducing the levels of the protein in the body.

# V. Use of Extended cDNAs or Portions Thereof as Reagents

The extended cDNAs of the present invention may be used as reagents in isolation procedures, diagnostic assays, and forensic procedures. For example, sequences from the extended cDNAs (or genomic DNAs obtainable 25 therefrom) may be detectably labeled and used as probes to isolate other sequences capable of hybridizing to them. In addition, sequences from the extended cDNAs (or genomic DNAs obtainable therefrom) may be used to design PCR primers to be used in isolation, diagnostic, or forensic procedures.

### **EXAMPLE 41**

# Preparation of PCR Primers and Amplification of DNA

The extended cDNAs (or genomic DNAs obtainable therefrom) may be used to prepare PCR primers for a 30 variety of applications, including isolation procedures for cloning nucleic acids capable of hybridizing to such sequences, diagnostic techniques and forensic techniques. The PCR primers are at least 10 bases, and preferably at least 12, 15, or 17 bases in length. More preferably, the PCR primers are at least 20-30 bases in length. In some embodiments, the PCR primers may be more than 30 bases in length. It is preferred that the primer pairs have approximately the same G/C

between the primer sites.



ratio, so that melting temperatures are approximately the same. A variety of PCR techniques are familiar to those skilled in the art. For a review of PCR technology, see Molecular Cloning to Genetic Engineering White, B.A. Ed. in Methods in Molecular Biology 67: Humana Press, Totowa 1997. In each of these PCR procedures, PCR primers on either side of the nucleic acid sequences to be amplified are added to a suitably prepared nucleic acid sample along with dNTPs and a thermostable polymerase such as Taq polymerase, Pfu polymerase, or Vent polymerase. The nucleic acid in the sample is denatured and the PCR primers are specifically hybridized to complementary nucleic acid sequences in the sample. The hybridized primers are extended. Thereafter, another cycle of denaturation, hybridization, and extension is initiated. The cycles are repeated multiple times to produce an amplified fragment containing the nucleic acid sequence

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### **EXAMPLE 42**

# Use of Extended cDNAs as Probes

Probes derived from extended cDNAs or portions thereof (or genomic DNAs obtainable therefrom) may be labeled with detectable labels familiar to those skilled in the art, including radioisotopes and non-radioactive labels, to provide a detectable probe. The detectable probe may be single stranded or double stranded and may be made using techniques known in the art, including in vitro transcription, nick translation, or kinase reactions. A nucleic acid sample containing a sequence capable of hybridizing to the labeled probe is contacted with the labeled probe. If the nucleic acid in the sample is double stranded, it may be denatured prior to contacting the probe. In some applications, the nucleic acid sample may be immobilized on a surface such as a nitrocellulose or nylon membrane. The nucleic acid sample may comprise nucleic acids obtained from a variety of sources, including genomic DNA, cDNA libraries, RNA, or tissue samples.

Procedures used to detect the presence of nucleic acids capable of hybridizing to the detectable probe include well known techniques such as Southern blotting, Northern blotting, dot blotting, colony hybridization, and plaque hybridization. In some applications, the nucleic acid capable of hybridizing to the labeled probe may be cloned into vectors such as expression vectors, sequencing vectors, or in vitro transcription vectors to facilitate the characterization and expression of the hybridizing nucleic acids in the sample. For example, such techniques may be used to isolate and clone sequences in a genomic library or cDNA library which are capable of hybridizing to the detectable probe as described in Example 30 above.

PCR primers made as described in Example 41 above may be used in forensic analyses, such as the DNA fingerprinting techniques described in Examples 43-47 below. Such analyses may utilize detectable probes or primers based on the sequences of the extended cDNAs isolated using the 5' ESTs (or genomic DNAs obtainable therefrom).

### **EXAMPLE 43**

# Forensic Matching by DNA Sequencing

In one exemplary method, DNA samples are isolated from forensic specimens of, for example, hair, semen, blood or skin cells by conventional methods. A panel of PCR primers based on a number of the extended cDNAs (or

genomic DNAs obtainable therefrom), is then utilized in accordance with Example 41 to amplify DNA of approximately 100-200 bases in length from the forensic specimen. Corresponding sequences are obtained from a test subject. Each of these identification DNAs is then sequenced using standard techniques, and a simple database comparison determines the differences, if any, between the sequences from the subject and those from the sample. Statistically significant differences between the suspect's DNA sequences and those from the sample conclusively prove a lack of identity. This lack of identity can be proven, for example, with only one sequence. Identity, on the other hand, should be demonstrated with a large number of sequences, all matching. Preferably, a minimum of 50 statistically identical sequences of 100 bases in length are used to prove identity between the suspect and the sample.

### **EXAMPLE 44**

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## Positive Identification by DNA Sequencing

The technique outlined in the previous example may also be used on a larger scale to provide a unique fingerprint-type identification of any individual. In this technique, primers are prepared from a large number of sequences from Table IV and the appended sequence listing. Preferably, 20 to 50 different primers are used. These primers are used to obtain a corresponding number of PCR-generated DNA segments from the individual in question in accordance with Example 41. Each of these DNA segments is sequenced, using the methods set forth in Example 43. The database of sequences generated through this procedure uniquely identifies the individual from whom the sequences were obtained. The same panel of primers may then be used at any later time to absolutely correlate tissue or other biological specimen with that individual.

### **EXAMPLE 45**

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## Southern Blot Forensic Identification

The procedure of Example 44 is repeated to obtain a panel of at least 10 amplified sequences from an individual and a specimen. Preferably, the panel contains at least 50 amplified sequences. More preferably, the panel contains 100 amplified sequences. In some embodiments, the panel contains 200 amplified sequences. This PCR-generated DNA is then digested with one or a combination of, preferably, four base specific restriction enzymes. Such enzymes are commercially available and known to those of skill in the art. After digestion, the resultant gene fragments are size separated in multiple duplicate wells on an agarose gel and transferred to nitrocellulose using Southern blotting techniques well known to those with skill in the art. For a review of Southern blotting see Davis et al. (Basic Methods in Molecular Biology, 1986, Elsevier Press. pp 62-65).

A panel of probes based on the sequences of the extended cDNAs (or genomic DNAs obtainable therefrom), or fragments thereof of at least 10 bases, are radioactively or colorimetrically labeled using methods known in the art, such as nick translation or end labeling, and hybridized to the Southern blot using techniques known in the art (Davis et al., supra). Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). More preferably, the probe comprises at least 20-30 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In some embodiments, the probe comprises more than 30



nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom).

Preferably, at least 5 to 10 of these labeled probes are used, and more preferably at least about 20 or 30 are used to provide a unique pattern. The resultant bands appearing from the hybridization of a large sample of extended cDNAs (or genomic DNAs obtainable therefrom) will be a unique identifier. Since the restriction enzyme cleavage will be different for every individual, the band pattern on the Southern blot will also be unique. Increasing the number of extended cDNA probes will provide a statistically higher level of confidence in the identification since there will be an increased number of sets of bands used for identification.

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### **EXAMPLE 46**

# **Dot Blot Identification Procedure**

Another technique for identifying individuals using the extended cDNA sequences disclosed herein utilizes a dot blot hybridization technique.

Genomic DNA is isolated from nuclei of subject to be identified. Oligonucleotide probes of approximately 30 bp
in length are synthesized that correspond to at least 10, preferably 50 sequences from the extended cDNAs or genomic
DNAs obtainable therefrom. The probes are used to hybridize to the genomic DNA through conditions known to those in
the art. The oligonucleotides are end labeled with P32 using polynucleotide kinase (Pharmacia). Dot Blots are created by
spotting the genomic DNA onto nitrocellulose or the like using a vacuum dot blot manifold (BioRad, Richmond California).
The nitrocellulose filter containing the genomic sequences is baked or UV linked to the filter, prehybridized and
hybridized with labeled probe using techniques known in the art (Davis et al. supra). The 32P labeled DNA fragments are
sequentially hybridized with successively stringent conditions to detect minimal differences between the 30 bp sequence
and the DNA. Tetramethylammonium chloride is useful for identifying clones containing small numbers of nucleotide
mismatches (Wood et al., Proc. Natl. Acad. Sci. USA 82(6):1585-1588 (1985)). A unique pattern of dots distinguishes
one individual from another individual.

Extended cDNAs or oligonucleotides containing at least 10 consecutive bases from these sequences can be used as probes in the following alternative fingerprinting technique. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). More preferably, the probe comprises at least 20-30 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In some embodiments, the probe comprises more than 30 nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom).



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Preferably, a plurality of probes having sequences from different genes are used in the alternative fingerprinting technique. Example 47 below provides a representative alternative fingerprinting procedure in which the probes are derived from extended cDNAs.

#### **EXAMPLE 47**

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### Alternative "Fingerprint" Identification Technique

20-mer oligonucleotides are prepared from a large number, e.g. 50, 100, or 200, of extended cDNA sequences (or genomic DNAs obtainable therefrom) using commercially available oligonucleotide services such as Genset, Paris, France. Cell samples from the test subject are processed for DNA using techniques well known to those with skill in the art. The nucleic acid is digested with restriction enzymes such as EcoRI and XbaI. Following digestion, samples are applied to wells for electrophoresis. The procedure, as known in the art, may be modified to accommodate polyacrylamide electrophoresis, however in this example, samples containing 5 ug of DNA are loaded into wells and separated on 0.8% agarose gels. The gels are transferred onto nitrocellulose using standard Southern blotting techniques.

10 ng of each of the oligonucleotides are pooled and end-labeled with P<sup>32</sup>. The nitrocellulose is prehybridized
with blocking solution and hybridized with the labeled probes. Following hybridization and washing, the nitrocellulose
filter is exposed to X-Omat AR X-ray film. The resulting hybridization pattern will be unique for each individual.

It is additionally contemplated within this example that the number of probe sequences used can be varied for additional accuracy or clarity.

The antibodies generated in Examples 30 and 40 above may be used to identify the tissue type or cell species from which a sample is derived as described above.

#### **EXAMPLE 48**

### Identification of Tissue Types or Cell Species by Means of

### Labeled Tissue Specific Antibodies

Identification of specific tissues is accomplished by the visualization of tissue specific antigens by means of
antibody preparations according to Examples 30 and 40 which are conjugated, directly or indirectly to a detectable
marker. Selected labeled antibody species bind to their specific antigen binding partner in tissue sections, cell
suspensions, or in extracts of soluble proteins from a tissue sample to provide a pattern for qualitative or semiqualitative interpretation.

Antisera for these procedures must have a potency exceeding that of the native preparation, and for that reason, antibodies are concentrated to a mg/ml level by isolation of the gamma globulin fraction, for example, by ion-exchange chromatography or by ammonium sulfate fractionation. Also, to provide the most specific antisera, unwanted antibodies, for example to common proteins, must be removed from the gamma globulin fraction, for example by means of insoluble immunoabsorbents, before the antibodies are labeled with the marker. Either monoclonal or heterologous antisera is suitable for either procedure.





Purified, high-titer antibodies, prepared as described above, are conjugated to a detectable marker, as described, for example, by Fudenberg, H., Chap. 26 in: **Basic 503 Clinical Immunology**, 3rd Ed. Lange, Los Altos, California (1980) or Rose, N. et al., Chap. 12 in: **Methods in Immunodiagnosis**, 2d Ed. John Wiley 503 Sons, New York (1980).

A fluorescent marker, either fluorescein or rhodamine, is preferred, but antibodies can also be labeled with an enzyme that supports a color producing reaction with a substrate, such as horseradish peroxidase. Markers can be added to tissue-bound antibody in a second step, as described below. Alternatively, the specific antitissue antibodies can be labeled with ferritin or other electron dense particles, and localization of the ferritin coupled antigen-antibody complexes achieved by means of an electron microscope. In yet another approach, the antibodies are radiolabeled, with, for example 1251, and detected by overlaying the antibody treated preparation with photographic emulsion.

Preparations to carry out the procedures can comprise monoclonal or polyclonal antibodies to a single protein or peptide identified as specific to a tissue type, for example, brain tissue, or antibody preparations to several antigenically distinct tissue specific antigens can be used in panels, independently or in mixtures, as required.

Tissue sections and cell suspensions are prepared for immunohistochemical examination according to common histological techniques. Multiple cryostat sections (about 4 µm, unfixed) of the unknown tissue and known control, are mounted and each slide covered with different dilutions of the antibody preparation. Sections of known and unknown tissues should also be treated with preparations to provide a positive control, a negative control, for example, pre-immune sera, and a control for non-specific staining, for example, buffer.

Treated sections are incubated in a humid chamber for 30 min at room temperature, rinsed, then washed in buffer for 30-45 min. Excess fluid is blotted away, and the marker developed.

If the tissue specific antibody was not labeled in the first incubation, it can be labeled at this time in a second antibody-antibody reaction, for example, by adding fluorescein- or enzyme-conjugated antibody against the immunoglobulin class of the antiserum-producing species, for example, fluorescein labeled antibody to mouse IgG. Such labeled sera are commercially available.

The antigen found in the tissues by the above procedure can be quantified by measuring the intensity of color or fluorescence on the tissue section, and calibrating that signal using appropriate standards.

### B. Identification of Tissue Specific Soluble Proteins

The visualization of tissue specific proteins and identification of unknown tissues from that procedure is

carried out using the labeled antibody reagents and detection strategy as described for immunohistochemistry; however
the sample is prepared according to an electrophoretic technique to distribute the proteins extracted from the tissue in
an orderly array on the basis of molecular weight for detection.

A tissue sample is homogenized using a Virtis apparatus; cell suspensions are disrupted by Dounce homogenization or osmotic lysis, using detergents in either case as required to disrupt cell membranes, as is the practice

in the art. Insoluble cell components such as nuclei, microsomes, and membrane fragments are removed by ultracentrifugation, and the soluble protein-containing fraction concentrated if necessary and reserved for analysis.

A sample of the soluble protein solution is resolved into individual protein species by conventional SDS polyacrylamide electrophoresis as described, for example, by Davis, L. et al., Section 19-2 in: Basic Methods in 5 Molecular Biology (P. Leder, ed), Elsevier, New York (1986), using a range of amounts of polyacrylamide in a set of gels to resolve the entire molecular weight range of proteins to be detected in the sample. A size marker is run in parallel for purposes of estimating molecular weights of the constituent proteins. Sample size for analysis is a convenient volume of from 5 to 55  $\mu$ l, and containing from about 1 to 100  $\mu$ g protein. An aliquot of each of the resolved proteins is transferred by blotting to a nitrocellulose filter paper, a process that maintains the pattern of resolution. Multiple copies are prepared. The procedure, known as Western Blot Analysis, is well described in Davis, L. et al., (above) Section 19-3. One set of nitrocellulose blots is stained with Coomassie Blue dye to visualize the entire set of proteins for comparison with the antibody bound proteins. The remaining nitrocellulose filters are then incubated with a solution of one or more specific antisera to tissue specific proteins prepared as described in Examples 30 and 40. In this procedure, as in procedure A above, appropriate positive and negative sample and reagent controls are run.

In either procedure A or B, a detectable label can be attached to the primary tissue antigen-primary antibody complex according to various strategies and permutations thereof. In a straightforward approach, the primary specific antibody can be labeled; alternatively, the unlabeled complex can be bound by a labeled secondary anti-IgG antibody. In other approaches, either the primary or secondary antibody is conjugated to a biotin molecule, which can, in a subsequent step, bind an avidin conjugated marker. According to yet another strategy, enzyme labeled or radioactive 20 protein A, which has the property of binding to any IgG, is bound in a final step to either the primary or secondary antibody.

The visualization of tissue specific antigen binding at levels above those seen in control tissues to one or more tissue specific antibodies, prepared from the gene sequences identified from extended cDNA sequences, can identify tissues of unknown origin, for example, forensic samples, or differentiated tumor tissue that has metastasized to foreign 25 bodily sites.

In addition to their applications in forensics and identification, extended cDNAs (or genomic DNAs obtainable therefrom) may be mapped to their chromosomal locations. Example 49 below describes radiation hybrid (RH) mapping of human chromosomal regions using extended cDNAs. Example 50 below describes a representative procedure for mapping an extended cDNA (or a genomic DNA obtainable therefrom) to its location on a human chromosome. Example 30 51 below describes mapping of extended cDNAs (or genomic DNAs obtainable therefrom) on metaphase chromosomes by Fluorescence In Situ Hybridization (FISH).

#### **EXAMPLE 49**

Radiation hybrid mapping of Extended cDNAs to the human genome



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Radiation hybrid (RH) mapping is a somatic cell genetic approach that can be used for high resolution mapping of the human genome. In this approach, cell lines containing one or more human chromosomes are lethally irradiated, breaking each chromosome into fragments whose size depends on the radiation dose. These fragments are rescued by fusion with cultured rodent cells, yielding subclones containing different portions of the human genome. This technique is described by Benham et al. (*Genomics* 4:509-517, 1989) and Cox et al., (*Science* 250:245-250, 1990). The random and independent nature of the subclones permits efficient mapping of any human genome marker. Human DNA isolated from a panel of 80-100 cell lines provides a mapping reagent for ordering extended cDNAs (or genomic DNAs obtainable therefrom). In this approach, the frequency of breakage between markers is used to measure distance, allowing construction of fine resolution maps as has been done using conventional ESTs (Schuler et al., *Science* 274:540-546, 1996).

RH mapping has been used to generate a high-resolution whole genome radiation hybrid map of human chromosome 17q22-q25.3 across the genes for growth hormone (GH) and thyr idine kinase (TK) (Foster et al., *Genomics* 33:185-192, 1996), the region surrounding the Gorlin syndrome gene (Obermayr et al., *Eur. J. Hum. Genet.* 4:242-245, 1996), 60 loci covering the entire short arm of chromosome 12 (Raeymaekers et al., *Genomics* 29:170-178, 1995), the region of human chromosome 22 containing the neurofibromatosis type 2 locus (Frazer et al., *Genomics* 14:574-584, 1992) and 13 loci on the long arm of chromosome 5 (Warrington et al., *Genomics* 11:701-708, 1991).

#### **EXAMPLE 50**

### Mapping of Extended cDNAs to Human

### Chromosomes using PCR techniques

Extended cDNAs (or genomic DNAs obtainable therefrom) may be assigned to human chromosomes using PCR based methodologies. In such approaches, oligonucleotide primer pairs are designed from the extended cDNA sequence (or the sequence of a genomic DNA obtainable therefrom) to minimize the chance of amplifying through an intron. Preferably, the oligonucleotide primers are 18-23 bp in length and are designed for PCR amplification. The creation of PCR primers from known sequences is well known to those with skill in the art. For a review of PCR technology see Erlich, H.A., PCR Technology: Principles and Applications for DNA Amplification. 1992. W.H. Freeman and Co., New York.

The primers are used in polymerase chain reactions (PCR) to amplify templates from total human genomic DNA. PCR conditions are as follows: 60 ng of genomic DNA is used as a template for PCR with 80 ng of each oligonucleotide primer, 0.6 unit of Taq polymerase, and 1  $\mu$ Cu of a <sup>32</sup>P-labeled deoxycytidine triphosphate. The PCR is performed in a microplate thermocycler (Techne) under the following conditions: 30 cycles of 94°C, 1.4 min; 55°C, 2 min; and 72°C, 2 min; with a final extension at 72°C for 10 min. The amplified products are analyzed on a 6% polyacrylamide sequencing gel and visualized by autoradiography. If the length of the resulting PCR product is identical to the distance between the ends of the primer sequences in the extended cDNA from which the primers are derived, then the PCR reaction is repeated with DNA templates from two panels of human-rodent somatic cell hybrids, BIOS

PCRable DNA (BIOS Corporation) and NIGMS Human-Rodent Somatic Cell Hybrid Mapping Panel Number 1 (NIGMS, Camden, NJ).

PCR is used to screen a series of somatic cell hybrid cell lines containing defined sets of human chromosomes for the presence of a given extended cDNA (or genomic DNA obtainable therefrom). DNA is isolated from the somatic hybrids and used as starting templates for PCR reactions using the primer pairs from the extended cDNAs (or genomic DNAs obtainable therefrom). Only those somatic cell hybrids with chromosomes containing the human gene corresponding to the extended cDNA (or genomic DNA obtainable therefrom) will yield an amplified fragment. The extended cDNAs (or genomic DNAs obtainable therefrom) are assigned to a chromosome by analysis of the segregation pattern of PCR products from the somatic hybrid DNA templates. The single human chromosome present in all cell hybrids that give rise to an amplified fragment is the chromosome containing that extended cDNA (or genomic DNA obtainable therefrom). For a review of techniques and analysis of results from somatic cell gene mapping experiments. (See Ledbetter et al., Genomics 6:475-481 (1990).)

Alternatively, the extended cDNAs (or genomic DNAs obtainable therefrom) may be mapped to individual chromosomes using FISH as described in Example 51 below.

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#### **EXAMPLE 51**

### Mapping of Extended 5' ESTs to Chromosomes

### Using Fluorescence in situ Hybridization

Fluorescence in situ hybridization allows the extended cDNA (or genomic DNA obtainable therefrom) to be mapped to a particular location on a given chromosome. The chromosomes to be used for fluorescence in situ hybridization techniques may be obtained from a variety of sources including cell cultures, tissues, or whole blood.

In a preferred embodiment, chromosomal localization of an extended cDNA (or genomic DNA obtainable therefrom) is obtained by FISH as described by Cherif et al. (*Proc. Natl. Acad. Sci. U.S.A.*, 87:6639-6643, 1990).

Metaphase chromosomes are prepared from phytohemagglutinin (PHA)-stimulated blood cell donors. PHA-stimulated lymphocytes from healthy males are cultured for 72 h in RPMI-1640 medium. For synchronization, methotrexate (10 µM) is added for 17 h, followed by addition of 5-bromodeoxyuridine (5-BudR, 0.1 mM) for 6 h. Colcemid (1 µg/ml) is added for the last 15 min before harvesting the cells. Cells are collected, washed in RPMI, incubated with a hypotonic solution of KCl (75 mM) at 37°C for 15 min and fixed in three changes of methanol:acetic acid (3:1). The cell suspension is dropped onto a glass slide and air dried. The extended cDNA (or genomic DNA obtainable therefrom) is labeled with biotin-16 dUTP by nick translation according to the manufacturer's instructions (Bethesda Research Just prior to hybridization, the DNA pellet is dissolved in hybridization buffer (50% formamide, 2 X SSC, 10% dextran sulfate, 1 mg/ml sonicated salmon sperm DNA, pH 7) and the probe is denatured at 70°C for 5-10 min.

Slides kept at -20°C are treated for 1 h at 37°C with RNase A (100  $\mu$ g/ml), rinsed three times in 2 X SSC and dehydrated in an ethanol series. Chromosome preparations are denatured in 70% formamide, 2 X SSC for 2 min at



70°C, then dehydrated at 4°C. The slides are treated with proteinase K (10 μg/100 ml in 20 mM Tris-HCl, 2 mM CaCl<sub>2</sub>) at 37°C for 8 min and dehydrated. The hybridization mixture containing the probe is placed on the slide, covered with a coverslip, sealed with rubber cement and incubated overnight in a humid chamber at 37°C. After hybridization and post-hybridization washes, the biotinylated probe is detected by avidin-FITC and amplified with additional layers of biotinylated goat anti-avidin and avidin-FITC. For chromosomal localization, fluorescent R-bands are obtained as previously described (Cherif et al., *supra.*). The slides are observed under a LEICA fluorescence microscope (DMRXA).

Chromosomes are counterstained with propidium iodide and the fluorescent signal of the probe appears as two symmetrical yellow-green spots on both chromatids of the fluorescent R-band chromosome (red). Thus, a particular extended cDNA (or genomic DNA obtainable therefrom) may be localized to a particular cytogenetic R-band on a given chromosome.

Once the extended cDNAs (or genomic DNAs obtainable therefrom) have been assigned to particular chromosomes using the techniques described in Examples 49-51 above, they may be utilized to construct a high resolution map of the chromosomes on which they are located or to identify the chromosomes in a sample.

#### **EXAMPLE 52**

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### Use of Extended cDNAs to Construct or Expand Chromosome Maps

Chromosome mapping involves assigning a given unique sequence to a particular chromosome as described above. Once the unique sequence has been mapped to a given chromosome, it is ordered relative to other unique sequences located on the same chromosome. One approach to chromosome mapping utilizes a series of yeast artificial chromosomes (YACs) bearing several thousand long inserts derived from the chromosomes of the organism from which the extended cDNAs (or genomic DNAs obtainable therefrom) are obtained. This approach is described in Ramaiah Nagaraja et al. Genome Research 7:210-222, March 1997. Briefly, in this approach each chromosome is broken into overlapping pieces which are inserted into the YAC vector. The YAC inserts are screened using PCR or other methods to determine whether they include the extended cDNA (or genomic DNA obtainable therefrom) whose position is to be determined. Once an insert has been found which includes the extended cDNA (or genomic DNA obtainable therefrom), the insert can be analyzed by PCR or other methods to determine whether the insert also contains other sequences known to be on the chromosome or in the region from which the extended cDNA (or genomic DNA obtainable therefrom) was derived. This process can be repeated for each insert in the YAC library to determine the location of each of the extended cDNAs (or genomic DNAs obtainable therefrom) relative to one another and to other known chromosomal markers. In this way, a high resolution map of the distribution of numerous unique markers along each of the organisms

As described in Example 53 below extended cDNAs (or genomic DNAs obtainable therefrom) may also be used to identify genes associated with a particular phenotype, such as hereditary disease or drug response.

#### **EXAMPLE 53**

Identification of genes associated with hereditary diseases or drug response

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This example illustrates an approach useful for the association of extended cDNAs (or genomic DNAs obtainable therefrom) with particular phenotypic characteristics. In this example, a particular extended cDNA (or genomic DNA obtainable therefrom) is used as a test probe to associate that extended cDNA (or genomic DNA obtainable therefrom) with a particular phenotypic characteristic.

Extended cDNAs (or genomic DNAs obtainable therefrom) are mapped to a particular location on a human chromosome using techniques such as those described in Examples 49 and 50 or other techniques known in the art. A search of Mendelian Inheritance in Man (V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) reveals the region of the human chromosome which contains the extended cDNA (or genomic DNA obtainable therefrom) to be a very gene rich region containing several known genes and several 10 diseases or phenotypes for which genes have not been identified. The gene corresponding to this extended cDNA (or genomic DNA obtainable therefrom) thus becomes an immediate candidate for each of these genetic diseases.

Cells from patients with these diseases or phenotypes are isolated and expanded in culture. PCR primers from the extended cDNA (or genomic DNA obtainable therefrom) are used to screen genomic DNA, mRNA or cDNA obtained from the patients. Extended cDNAs (or genomic DNAs obtainable therefrom) that are not amplified in the patients can 15 be positively associated with a particular disease by further analysis. Alternatively, the PCR analysis may yield fragments of different lengths when the samples are derived from an individual having the phenotype associated with the disease than when the sample is derived from a healthy individual, indicating that the gene containing the extended cDNA may be responsible for the genetic disease.

### VI. Use of Extended cDNAs (or genomic DNAs obtainable therefrom) to Construct Vectors

The present extended cDNAs (or genomic DNAs obtainable therefrom) may also be used to construct secretion vectors capable of directing the secretion of the proteins encoded by genes inserted in the vectors. Such secretion vectors may facilitate the purification or enrichment of the proteins encoded by genes inserted therein by reducing the number of background proteins from which the desired protein must be purified or enriched. Exemplary secretion vectors are described in Example 54 below.

#### **EXAMPLE 54**

#### Construction of Secretion Vectors

The secretion vectors of the present invention include a promoter capable of directing gene expression in the host cell, tissue, or organism of interest. Such promoters include the Rous Sarcoma Virus promoter, the SV40 promoter, the human cytomegalovirus promoter, and other promoters familiar to those skilled in the art.

A signal sequence from an extended cDNA (or genomic DNA obtainable therefrom), such as one of the signal sequences in SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above, is operably linked to the promoter such that the mRNA transcribed from the promoter will direct the translation of the signal peptide. The host cell, tissue, or organism may be any cell, tissue, or organism which recognizes the signal peptide encoded by the signal sequence in the





extended cDNA (or genomic DNA obtainable therefrom). Suitable hosts include mammalian cells, tissues or organisms, avian cells, tissues, or organisms, insect cells, tissues or organisms, or yeast.

In addition, the secretion vector contains cloning sites for inserting genes encoding the proteins which are to be secreted. The cloning sites facilitate the cloning of the insert gene in frame with the signal sequence such that a fusion protein in which the signal peptide is fused to the protein encoded by the inserted gene is expressed from the mRNA transcribed from the promoter. The signal peptide directs the extracellular secretion of the fusion protein.

The secretion vector may be DNA or RNA and may integrate into the chromosome of the host, be stably maintained as an extrachromosomal replicon in the host, be an artificial chromosome, or be transiently present in the host. Many nucleic acid backbones suitable for use as secretion vectors are known to those skilled in the art, including retroviral vectors, SV40 vectors, Bovine Papilloma Virus vectors, yeast integrating plasmids, yeast episomal plasmids, yeast artificial chromosomes, human artificial chromosomes, P element vectors, baculovirus vectors, or bacterial plasmids capable of being transiently introduced into the host.

The secretion vector may also contain a polyA signal such that the polyA signal is located downstream of the gene inserted into the secretion vector.

After the gene encoding the protein for which secretion is desired is inserted into the secretion vector, the secretion vector is introduced into the host cell, tissue, or organism using calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection, viral particles or as naked DNA. The protein encoded by the inserted gene is then purified or enriched from the supernatant using conventional techniques such as ammonium sulfate precipitation, immunoprecipitation, immunochromatography, size exclusion chromatography, ion exchange chromatography, and hplc. Alternatively, the secreted protein may be in a sufficiently enriched or pure state in the supernatant or growth media of the host to permit it to be used for its intended purpose without further enrichment.

The signal sequences may also be inserted into vectors designed for gene therapy. In such vectors, the signal sequence is operably linked to a promoter such that mRNA transcribed from the promoter encodes the signal peptide. A cloning site is located downstream of the signal sequence such that a gene encoding a protein whose secretion is desired may readily be inserted into the vector and fused to the signal sequence. The vector is introduced into an appropriate host cell. The protein expressed from the promoter is secreted extracellularly, thereby producing a therapeutic effect.

The extended cDNAs or 5' ESTs may also be used to clone sequences located upstream of the extended cDNAs or 5' ESTs which are capable of regulating gene expression, including promoter sequences, enhancer sequences, and other upstream sequences which influence transcription or translation levels. Once identified and cloned, these upstream regulatory sequences may be used in expression vectors designed to direct the expression of an inserted gene in a desired spatial, temporal, developmental, or quantitative fashion. Example 55 describes a method for cloning sequences upstream of the extended cDNAs or 5' ESTs.

#### **EXAMPLE 55**

### Use of Extended cDNAs or 5' ESTs to Clone Upstream

### Sequences from Genomic DNA

Sequences derived from extended cDNAs or 5' ESTs may be used to isolate the promoters of the corresponding genes using chromosome walking techniques. In one chromosome walking technique, which utilizes the 5 GenomeWalker™ kit available from Clontech, five complete genomic DNA samples are each digested with a different restriction enzyme which has a 6 base recognition site and leaves a blunt end. Following digestion, oligonucleotide adapters are ligated to each end of the resulting genomic DNA fragments.

For each of the five genomic DNA libraries, a first PCR reaction is performed according to the manufacturer's instructions using an outer adaptor primer provided in the kit and an outer gene specific primer. The gene specific primer 10 should be selected to be specific for the extended cDNA or 5' EST of interest and should have a melting temperature, length, and location in the extended cDNA or 'EST which is consistent with its use in PCR reactions. Each first PCR reaction contains 5ng of genomic DNA, 5  $\mu$ l of 10X Tth reaction buffer, 0.2 mM of each dNTP, 0.2  $\mu$ M each of outer adaptor primer and outer gene specific primer, 1.1 mM of Mg(OAc)<sub>2</sub>, and 1  $\mu$ l of the Tth polymerase 50X mix in a total volume of 50  $\mu$ l. The reaction cycle for the first PCR reaction is as follows: 1 min @ 94°C / 2 sec @ 94°C, 3 min @ 15 72°C (7 cycles) / 2 sec @ 94°C, 3 min @ 67°C (32 cycles) / 5 min @ 67°C.

The product of the first PCR reaction is diluted and used as a template for a second PCR reaction according to the manufacturer's instructions using a pair of nested primers which are located internally on the amplicon resulting from the first PCR reaction. For example, 5  $\mu$ l of the reaction product of the first PCR reaction mixture may be diluted 180 times. Reactions are made in a 50  $\mu$ l volume having a composition identical to that of the first PCR reaction except 20 the nested primers are used. The first nested primer is specific for the adaptor, and is provided with the GenomeWalker<sup>TM</sup> kit. The second nested primer is specific for the particular extended cDNA or 5' EST for which the promoter is to be cloned and should have a melting temperature, length, and location in the extended cDNA or 5' EST which is consistent with its use in PCR reactions. The reaction parameters of the second PCR reaction are as follows: 1 min @ 94°C / 2 sec @ 94°C, 3 min @ 72°C (6 cycles) / 2 sec @ 94°C, 3 min @ 67°C (25 cycles) / 5 min @ 67°C

The product of the second PCR reaction is purified, cloned, and sequenced using standard techniques. Alternatively, two or more human genomic DNA libraries can be constructed by using two or more restriction enzymes. The digested genomic DNA is cloned into vectors which can be converted into single stranded, circular, or linear DNA. A biotinylated oligonucleotide comprising at least 15 nucleotides from the extended cDNA or 5' EST sequence is hybridized to the single stranded DNA. Hybrids between the biotinylated oligonucleotide and the single stranded DNA containing 30 the extended cDNA or EST sequence are isolated as described in Example 29 above. Thereafter, the single stranded DNA containing the extended cDNA or EST sequence is released from the beads and converted into double stranded DNA using a primer specific for the extended cDNA or 5' EST sequence or a primer corresponding to a sequence included in the cloning vector. The resulting double stranded DNA is transformed into bacteria. DNAs containing the 5' EST or extended cDNA sequences are identified by colony PCR or colony hybridization.





Once the upstream genomic sequences have been cloned and sequenced as described above, prospective promoters and transcription start sites within the upstream sequences may be identified by comparing the sequences upstream of the extended cDNAs or 5' ESTs with databases containing known transcription start sites, transcription factor binding sites, or promoter sequences.

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5 In addition, promoters in the upstream sequences may be identified using promoter reporter vectors as described in Example 56.

#### **EXAMPLE 56**

### Identification of Promoters in Cloned Upstream Sequences

The genomic sequences upstream of the extended cDNAs or 5' ESTs are cloned into a suitable promoter 10 reporter vector, such as the pSEAP-Basic, pSEAP-Enhancer, pβgal-Basic, pβgal-Enhancer, or pEGFP-1 Promoter Reporter vectors available from Clontech. Briefly, each of these promoter reporter vectors include multiple cloning sites positioned upstream of a reporter gene encoding a readily assayable protein such as secreted alkaline phosphatase,  $\beta$ galactosidase, or green fluorescent protein. The sequences upstream of the extended cDNAs or 5' ESTs are inserted into the cloning sites upstream of the reporter gene in both orientations and introduced into an appropriate host cell. The 15 level of reporter protein is assayed and compared to the level obtained from a vector which lacks an insert in the cloning site. The presence of an elevated expression level in the vector containing the insert with respect to the control vector indicates the presence of a promoter in the insert. If necessary, the upstream sequences can be cloned into vectors which contain an enhancer for augmenting transcription levels from weak promoter sequences. A significant level of expression above that observed with the vector lacking an insert indicates that a promoter sequence is present in the inserted upstream sequence. 20

Appropriate host cells for the promoter reporter vectors may be chosen based on the results of the above described determination of expression patterns of the extended cDNAs and ESTs. For example, if the expression pattern analysis indicates that the mRNA corresponding to a particular extended cDNA or 5' EST is expressed in fibroblasts, the promoter reporter vector may be introduced into a human fibroblast cell line.

Promoter sequences within the upstream genomic DNA may be further defined by constructing nested deletions in the upstream DNA using conventional techniques such as Exonuclease III digestion. The resulting deletion fragments can be inserted into the promoter reporter vector to determine whether the deletion has reduced or obliterated promoter activity. In this way, the boundaries of the promoters may be defined. If desired, potential individual regulatory sites within the promoter may be identified using site directed mutagenesis or linker scanning to obliterate 30 potential transcription factor binding sites within the promoter individually or in combination. The effects of these mutations on transcription levels may be determined by inserting the mutations into the cloning sites in the promoter reporter vectors.

### **EXAMPLE 57**

### Cloning and Identification of Promoters

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Using the method described in Example 55 above with 5' ESTs, sequences upstream of several genes were obtained. Using the primer pairs GGG AAG ATG GAG ATA GTA TTG CCT G (SEQ ID NO:29) and CTG CCA TGT ACA TGA TAG AGA GAT TC (SEQ ID NO:30), the promoter having the internal designation P13H2 (SEQ ID NO:31) was obtained.

Using the primer pairs GTA CCA GGGG ACT GTG ACC ATT GC (SEQ ID NO:32) and CTG TGA CCA TTG CTC CCA AGA GAG (SEQ ID NO:33), the promoter having the internal designation P15B4 (SEQ ID NO:34) was obtained.

Using the primer pairs CTG GGA TGG AAG GCA CGG TA (SEQ ID NO:35) and GAG ACC ACA CAG CTA GAC AA (SEQ ID NO:36), the promoter having the internal designation P2986 (SEQ ID NO:37) was obtained.

Figure 8 provides a schematic description of the promoters isolated and the way they are assembled with the corresponding 5' tags. The upstream sequences were screened for the presence of motifs resembling transcription factor binding sites or known transcription start sites using the computer program MatInspector release 2.0, August 1996.

Figure 9 describes the transcription factor binding sites present in each of these promoters. The columns labeled matrice provides the name of the MatInspector matrix used. The column labeled position provides the 5' postion of the promoter site. Numeration of the sequence starts from the transcription site as determined by matching the genomic sequence with the 5' EST sequence. The column labeled "orientation" indicates the DNA strand on which the site is found, with the + strand being the coding strand as determined by matching the genomic sequence with the sequence of the 5' EST. The column labeled "score" provides the MatInspector score found for this site. The column labeled "length" provides the length of the site in nucleotides. The column labeled "sequence" provides the sequence of the site found.

The promoters and other regulatory sequences located upstream of the extended cDNAs or 5' ESTs may be used to design expression vectors capable of directing the expression of an inserted gene in a desired spatial, temporal, developmental, or quantitative manner. A promoter capable of directing the desired spatial, temporal, developmental, and quantitative patterns may be selected using the results of the expression analysis described in Example 26 above. For example, if a promoter which confers a high level of expression in muscle is desired, the promoter sequence upstream of an extended cDNA or 5' EST derived from an mRNA which is expressed at a high level in muscle, as determined by the method of Example 26, may be used in the expression vector.

Preferably, the desired promoter is placed near multiple restriction sites to facilitate the cloning of the desired insert downstream of the promoter, such that the promoter is able to drive expression of the inserted gene. The promoter may be inserted in conventional nucleic acid backbones designed for extrachromosomal replication, integration into the host chromosomes or transient expression. Suitable backbones for the present expression vectors include retroviral backbones, backbones from eukaryotic episomes such as SV40 or Bovine Papilloma Virus, backbones from bacterial episomes, or artificial chromosomes.





Preferably, the expression vectors also include a polyA signal downstream of the multiple restriction sites for directing the polyadenylation of mRNA transcribed from the gene inserted into the expression vector.

Following the identification of promoter sequences using the procedures of Examples 55-57, proteins which interact with the promoter may be identified as described in Example 58 below.

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#### **EXAMPLE 58**

## Identification of Proteins Which Interact with Promoter Sequences, Upstream

#### Regulatory Sequences, or mRNA

Sequences within the promoter region which are likely to bind transcription factors may be identified by homology to known transcription factor binding sites or through conventional mutagenesis or deletion analyses of reporter plasmids containing the promoter sequence. For example, deletions may be made in a reporter plasmid containing the promoter sequence of interest operably linked to an assayable reporter gene. The reporter plasmids carrying various deletions within the promoter region are transfected into an appropriate host cell and the effects of the deletions on expression levels is assessed. Transcription factor binding sites within the regions in which deletions reduce expression levels may be further localized using site directed mutagenesis, linker scanning analysis, or other techniques familiar to those skilled in the art. Nucleic acids encoding proteins which interact with sequences in the promoter may be identified using one-hybrid systems such as those described in the manual accompanying the Matchmaker One-Hybrid System kit available from Clontech (Catalog No. K1603-1). Briefly, the Matchmaker One-hybrid system is used as follows. The target sequence for which it is desired to identify binding proteins is cloned upstream of a selectable reporter gene and integrated into the yeast genome. Preferably, multiple copies of the target sequences are inserted into the reporter plasmid in tandem.

A library comprised of fusions between cDNAs to be evaluated for the ability to bind to the promoter and the activation domain of a yeast transcription factor, such as GAL4, is transformed into the yeast strain containing the integrated reporter sequence. The yeast are plated on selective media to select cells expressing the selectable marker linked to the promoter sequence. The colonies which grow on the selective media contain genes encoding proteins which bind the target sequence. The inserts in the genes encoding the fusion proteins are further characterized by sequencing. In addition, the inserts may be inserted into expression vectors or in vitro transcription vectors. Binding of the polypeptides encoded by the inserts to the promoter DNA may be confirmed by techniques familiar to those skilled in the art, such as gel shift analysis or DNAse protection analysis.

# VII. Use of Extended cDNAs (or Genomic DNAs Obtainable Therefrom) in Gene Therapy

The present invention also comprises the use of extended cDNAs (or genomic DNAs obtainable therefrom) in gene therapy strategies, including antisense and triple helix strategies as described in Examples 57 and 58 below. In antisense approaches, nucleic acid sequences complementary to an mRNA are hybridized to the mRNA intracellularly, thereby blocking the expression of the protein encoded by the mRNA. The antisense sequences may prevent gene expression through a variety of mechanisms. For example, the antisense sequences may inhibit the ability of ribosomes

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to translate the mRNA. Alternatively, the antisense sequences may block transport of the mRNA from the nucleus to the cytoplasm, thereby limiting the amount of mRNA available for translation. Another mechanism through which antisense sequences may inhibit gene expression is by interfering with mRNA splicing. In yet another strategy, the antisense nucleic acid may be incorporated in a ribozyme capable of specifically cleaving the target mRNA.

**EXAMPLE 59** 

### Preparation and Use of Antisense Oligonucleotides

The antisense nucleic acid molecules to be used in gene therapy may be either DNA or RNA sequences. They may comprise a sequence complementary to the sequence of the extended cDNA (or genomic DNA obtainable therefrom). The antisense nucleic acids should have a length and melting temperature sufficient to permit formation of an intracellular duplex having sufficient stability to inhibit the expression of the mRNA in the duplex. Strategies for designing antisense nucleic acids suitable for use in gene therapy are disclosed in Green et al., Ann. Rev. Biochem. 55:569-597 (1986) and Izant and Weintraub, Cell 36:1007-1015 (1984).

In some strategies, antisense molecules are obtained from a nucleotide sequence encoding a protein by reversing the orientation of the coding region with respect to a promoter so as to transcribe the opposite strand from that which is normally transcribed in the cell. The antisense molecules may be transcribed using in vitro transcription systems such as those which employ T7 or SP6 polymerase to generate the transcript. Another approach involves transcription of the antisense nucleic acids in vivo by operably linking DNA containing the antisense sequence to a promoter in an expression vector.

Alternatively, oligonucleotides which are complementary to the strand normally transcribed in the cell may be synthesized in vitro. Thus, the antisense nucleic acids are complementary to the corresponding mRNA and are capable of hybridizing to the mRNA to create a duplex. In some embodiments, the antisense sequences may contain modified sugar phosphate backbones to increase stability and make them less sensitive to RNase activity. Examples of modifications suitable for use in antisense strategies are described by Rossi et al., Pharmacol. Ther. 50(2):245-254, (1991).

Various types of antisense oligonucleotides complementary to the sequence of the extended cDNA (or genomic DNA obtainable therefrom) may be used. In one preferred embodiment, stable and semi-stable antisense oligonucleotides described in International Application No. PCT W094/23026 are used. In these molecules, the 3' end or both the 3' and 5' ends are engaged in intramolecular hydrogen bonding between complementary base pairs. These molecules are better able to withstand exonuclease attacks and exhibit increased stability compared to conventional antisense oligonucleotides.

In another preferred embodiment, the antisense oligodeoxynucleotides against herpes simplex virus types 1 and 2 described in International Application No. WO 95/04141.

In yet another preferred embodiment, the covalently cross-linked antisense oligonucleotides described in International Application No. WO 96/31523 are used. These double- or single-stranded oligonucleotides comprise one or

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more, respectively, inter- or intra-oligonucleotide covalent cross-linkages, wherein the linkage consists of an amide bond between a primary amine group of one strand and a carboxyl group of the other strand or of the same strand, respectively, the primary amine group being directly substituted in the 2' position of the strand nucleotide monosaccharide ring, and the carboxyl group being carried by an aliphatic spacer group substituted on a nucleotide or nucleotide analog of the other strand or the same strand, respectively.

The antisense oligodeoxynucleotides and oligonucleotides disclosed in International Application No. WO
92/18522 may also be used. These molecules are stable to degradation and contain at least one transcription control recognition sequence which binds to control proteins and are effective as decoys therefor. These molecules may contain "hairpin" structures, "dumbbel!" structures, "modified dumbbel!" structures, "cross-linked" decoy structures and "loop"
10 structures.

In another preferred embodiment, the cyclic double-stranded oligonucleotides described in European Patent Application No. 0 572 287 A2 are used. These ligated oligonucleotide "dumbbells" contain the binding site for a transcription factor and inhibit expression of the gene under control of the transcription factor by sequestering the factor.

Use of the closed antisense oligonucleotides disclosed in International Application No. WO 92/19732 is also contemplated. Because these molecules have no free ends, they are more resistant to degradation by exonucleases than are conventional oligonucleotides. These oligonucleotides may be multifunctional, interacting with several regions which are not adjacent to the target mRNA.

The appropriate level of antisense nucleic acids required to inhibit gene expression may be determined using in vitro expression analysis. The antisense molecule may be introduced into the cells by diffusion, injection, infection or transfection using procedures known in the art. For example, the antisense nucleic acids can be introduced into the body as a bare or naked oligonucleotide, oligonucleotide encapsulated in lipid, oligonucleotide sequence encapsidated by viral protein, or as an oligonucleotide operably linked to a promoter contained in an expression vector. The expression vector may be any of a variety of expression vectors known in the art, including retroviral or viral vectors, vectors capable of extrachromosomal replication, or integrating vectors. The vectors may be DNA or RNA.

The antisense molecules are introduced onto cell samples at a number of different concentrations preferably between 1x10<sup>-10</sup>M to 1x10<sup>-4</sup>M. Once the minimum concentration that can adequately control gene expression is identified, the optimized dose is translated into a dosage suitable for use in vivo. For example, an inhibiting concentration in culture of 1x10<sup>-7</sup> translates into a dose of approximately 0.6 mg/kg bodyweight. Levels of oligonucleotide approaching 100 mg/kg bodyweight or higher may be possible after testing the toxicity of the oligonucleotide in laboratory animals. It is additionally contemplated that cells from the vertebrate are removed, treated with the antisense oligonucleotide, and reintroduced into the vertebrate.

It is further contemplated that the antisense oligonucleotide sequence is incorporated into a ribozyme sequence to enable the antisense to specifically bind and cleave its target mRNA. For technical applications of ribozyme and antisense oligonucleotides see Rossi et al., supra.

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In a preferred application of this invention, the polypeptide encoded by the gene is first identified, so that the effectiveness of antisense inhibition on translation can be monitored using techniques that include but are not limited to antibody-mediated tests such as RIAs and ELISA, functional assays, or radiolabeling.

The extended cDNAs of the present invention (or genomic DNAs obtainable therefrom) may also be used in gene therapy approaches based on intracellular triple helix formation. Triple helix oligonucleotides are used to inhibit transcription from a genome. They are particularly useful for studying alterations in cell activity as it is associated with 10 a particular gene. The extended cDNAs (or genomic DNAs obtainable therefrom) of the present invention or, more preferably, a portion of those sequences, can be used to inhibit gene expression in individuals having diseases associated with expression of a particular gene. Similarly, a portion of the extended cDNA (or genomic DNA obtainable therefrom) can be used to study the effect of inhibiting transcription of a particular gene within a cell. Traditionally, homopurine sequences were considered the most useful for triple helix strategies. However, homopyrimidine sequences can also 15 inhibit gene expression. Such homopyrimidine oligonucleotides bind to the major groove at homopyrimidine sequences. Thus, both types of sequences from the extended cDNA or from the gene corresponding to the extended cDNA are contemplated within the scope of this invention.

### **EXAMPLE 60**

### Preparation and use of Triple Helix Probes

The sequences of the extended cDNAs (or genomic DNAs obtainable therefrom) are scanned to identify 10-mer to 20-mer homopyrimidine or homopurine stretches which could be used in triple-helix based strategies for inhibiting gene expression. Following identification of candidate homopyrimidine or homopurine stretches, their efficiency in inhibiting gene expression is assessed by introducing varying amounts of oligonucleotides containing the candidate sequences into tissue culture cells which normally express the target gene. The oligonucleotides may be prepared on an oligonucleotide 25 synthesizer or they may be purchased commercially from a company specializing in custom oligonucleotide synthesis, such as GENSET, Paris, France.

The oligonucleotides may be introduced into the cells using a variety of methods known to those skilled in the art, including but not limited to calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection or native uptake.

Treated cells are monitored for altered cell function or reduced gene expression using techniques such as 30 Northern blotting, RNase protection assays, or PCR based strategies to monitor the transcription levels of the target gene in cells which have been treated with the oligonucleotide . The cell functions to be monitored are predicted based upon the homologies of the target gene corresponding to the extended cDNA from which the oligonucleotide was derived with known gene sequences that have been associated with a particular function. The cell functions can also be





predicted based on the presence of abnormal physiologies within cells derived from individuals with a particular inherited disease, particularly when the extended cDNA is associated with the disease using techniques described in Example 53.

The oligonucleotides which are effective in inhibiting gene expression in tissue culture cells may then be introduced in vivo using the techniques described above and in Example 59 at a dosage calculated based on the in vitro results, as described in Example 59.

In some embodiments, the natural (beta) anomers of the oligonucleotide units can be replaced with alpha anomers to render the oligonucleotide more resistant to nucleases. Further, an intercalating agent such as ethidium bromide, or the like, can be attached to the 3' end of the alpha oligonucleotide to stabilize the triple helix. For information on the generation of oligonucleotides suitable for triple helix formation see Griffin et al. (Science 245:967-10 971 (1989).

#### **EXAMPLE 61**

## Use of Extended cDNAs to Express an Encoded Protein in a Host Organism

The extended cDNAs of the present invention may also be used to express an encoded protein in a host organism to produce a beneficial effect. In such procedures, the encoded protein may be transiently expressed in the host organism or stably expressed in the host organism. The encoded protein may have any of the activities described above. The encoded protein may be a protein which the host organism lacks or, alternatively, the encoded protein may augment the existing levels of the protein in the host organism.

A full length extended cDNA encoding the signal peptide and the mature protein, or an extended cDNA encoding only the mature protein is introduced into the host organism. The extended cDNA may be introduced into the host organism using a variety of techniques known to those of skill in the art. For example, the extended cDNA may be injected into the host organism as naked DNA such that the encoded protein is expressed in the host organism, thereby producing a beneficial effect.

Alternatively, the extended cDNA may be cloned into an expression vector downstream of a promoter which is active in the host organism. The expression vector may be any of the expression vectors designed for use in gene therapy, including viral or retroviral vectors.

The expression vector may be directly introduced into the host organism such that the encoded protein is expressed in the host organism to produce a beneficial effect. In another approach, the expression vector may be introduced into cells in vitro. Cells containing the expression vector are thereafter selected and introduced into the host organism, where they express the encoded protein to produce a beneficial effect.

### **EXAMPLE 62**

## Use Of Signal Peptides Encoded By 5' Ests Or Sequences

### Obtained Therefrom To Import Proteins Into Cells

The short core hydrophobic region (h) of signal peptides encoded by the 5'ESTS or extended cDNAs derived from the 5'ESTs of the present invention may also be used as a carrier to import a peptide or a protein of interest, so-

called cargo, into tissue culture cells (Lin *et al., J. Biol. Chem.,* **270**: 14225-14258 (1995); Du *et al., J. Peptide Res.,* **51**: 235-243 (1998); Rojas *et al., Nature Biotech.,* **16**: 370-375 (1998)).

When ceii permeable peptides of limited size (approximately up to 25 amino acids) are to be translocated across cell membrane, chemical synthesis may be used in order to add the h region to either the C-terminus or the N-terminus to the cargo peptide of interest. Alternatively, when longer peptides or proteins are to be imported into cells, nucleic acids can be genetically engineered, using techniques familiar to those skilled in the art, in order to link the extended cDNA sequence encoding the h region to the 5' or the 3' end of a DNA sequence coding for a cargo polypeptide. Such genetically engineered nucleic acids are then translated either *in vitro* or *in vivo* after transfection into appropriate cells, using conventional techniques to produce the resulting cell permeable polypeptide. Suitable hosts cells are then simply incubated with the cell permeable polypeptide which is then translocated across the membrane.

This method may be applied to study diverse intracellular functions and cellular processes. For instance, it has been used to probe functionally relevant domains of intracellular proteins and to examine protein-protein interactions involved in signal transduction pathways (Lin et al., supra; Lin et al., J. Biol. Chem., 271: 5305-5308 (1996); Rojas et al., J. Biol. Chem., 271: 27456-27461 (1996); Liu et al., Proc. Natl. Acad. Sci. USA, 93: 11819-11824 (1996); Rojas et al., Bioch. Biophys. Res. Commun., 234: 675-680 (1997)).

Such techniques may be used in cellular therapy to import proteins producing therapeutic effects. For instance, cells isolated from a patient may be treated with imported therapeutic proteins and then re-introduced into the host organism.

Alternatively, the h region of signal peptides of the present invention could be used in combination with a

nuclear localization signal to deliver nucleic acids into cell nucleus. Such oligonucleotides may be antisense
oligonucleotides or oligonucleotides designed to form triple helixes, as described in examples 59 and 60 respectively, in
order to inhibit processing and maturation of a target cellular RNA.

#### **EXAMPLE 63**

### Reassembling & Resequencing of Clones

Full length cDNA clones obtained by the procedure described in Example 27 were double-sequenced. These sequences were assembled and the resulting consensus sequences were then reanalyzed. Open reading frames were reassigned following essentially the same process as the one described in Example 27.

After this reanalysis process a few abnormalities were revealed. The sequences presented in SEQ ID NOs: 47, 73, 79, 89, 91, 96, 126, 128, 134, and 139 are apparently unlikely to be genuine full length cDNAs. These clones are missing a stop codon and are thus more probably 3' truncated cDNA sequences. Similarly, the sequences presented in SEQ ID NOs: 45, 50, 54, 57, 73, 74, 89, 92, 95, 98, 126, 129, 130, 131 and 139 may also not be genuine full length cDNAs based on homology studies with existing protein sequences. Although both of these sequences encode a potential start methionine each could represent a 5' truncated cDNA.





In addition, SEQ ID NO: 115 was found to be an alternatively spliced transcript and the identities of some of the bases in SEQ ID NO: 131 were corrected.

Finally, after the reassignment of open reading frames for the clones, new open reading frames were chosen in some instances. For example, in the case of SEQ ID NOs: 41, 47, 50, 52, 54-56, 58, 59, 61, 74, 75, 79, 84, 89, 91, 92, 96, 98, 103, 105, 106, 126, 129, 131, and 133 the new open reading frames were no longer predicted to contain a signal peptide.

As discussed above, Table IV provides the sequence identification numbers of the extended cDNAs of the present invention, the locations of the full coding sequences in SEQ ID NOs: 40-140 and 242-377 (i.e. the nucleotides encoding both the signal peptide and the mature protein, listed under the heading FCS location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the signal peptides (listed under the heading SigPep Location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the mature proteins generated by cleavage of the signal peptides (listed under the heading Mature Polypeptide Location in Table IV), the locations in SEQ ID NOs: 40-140 and 242-377 of stop codons (listed under the heading Stop Codon Location in Table IV) the locations in SEQ ID NOs: 40-140 and 242-377 of polyA signals (listed under the heading g PolyA Signal Location in Table IV) and the locations of polyA sites (listed under the heading PolyA Site Location in Table IV).

As discussed above, Table V lists the sequence identification numbers of the polypeptides of SEQ ID NOs: 141-241 and 378-513 in the full length polypeptide (second column), the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the signal peptides (third column), and the locations of the amino acid residues of SEQ ID NOs: 141-241 and 379-513 in the mature polypeptide created by cleaving the signal peptide from the fall length polypeptide (fourth column). In Table V, and in the appended sequence listing, the first amino acid of the mature protein resulting from cleavage of the signal peptide is designated as amino acid number 1 and the first amino acid of the signal peptide is designated with the appropriate negative number, in accordance with the regulations governing sequence listings.

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#### **EXAMPLE 64**

### **Functional Analysis of Predicted Protein Sequences**

Following double-sequencing, new contigs were assembled for each of the extended cDNAs of the present invention and each was compared to known sequences available at the time of filing. These sequences originate from the following databases: Genbank (release 108 and daily releases up to October, 15, 1998), Genseq (release 32) PIR (release 30–53) and SwissProt (release 35). The predicted proteins of the present invention matching known proteins were further classified into 3 categories depending on the level of homology.

The first category contains proteins of the present invention exhibiting more than 70% identical amino acid residues on the whole length of the matched protein. They are clearly close homologues which most probably have the same function or a very similar function as the matched protein.

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The second category contains proteins of the present invention exhibiting more remote homologies (40 to 70% over the whole protein) indicating that the protein of the present inventionmay have functions similar to those of the homologous protein.

The third category contains proteins exhibiting homology (90 to 100%) to a domain of a known protein indicating that the matched protein and the protein of the invention may share similar features.

It should be noted that the numbering of amino acids in the protein sequences discussed in Figures 10 to 15, and Table VIII, the first methionine encountered is designated as amino acid number 1. In the appended sequence listing, the first amino acid of the mature protein resulting from cleavage of the signal peptide is designated as amino acid number 1, and the first amino acid of the signal peptide is designated with the appropriate negative number, in accordance with the regulations governing sequence listings.

In addition all of the corrected amino acid sequences (SEQ ED NOs: 141-241 and 378-513) were scanned for the presence of known protein signatures and motifs. This search was performed against the Prosite 15.0 database, using the Proscan software from the GCG package- Functional signatures and their locations are indicated in Table VIII.

### 15 A) Proteins which are closely related to known proteins

### Protein of SEQ ID NO: 217

The protein of SEQ ID NO: 217 encoded by the extended cDNA SEQ ID NO: 116 isolated from lymphocyte shows complete identity to a human protein TFAR19 that may play a role in apoptosis (Genbank accession number AF014955, SEQ ID NO: 516) as shown by the alignment in figure 10.

Taken together, these data suggest that the protein of SEQ ID NO: 217 may be involved in the control of development and homeostasis. Thus, this protein may be useful in diagnosis and/or treating several types of disorders including, but not limited to, cancer, autoimmune disorders, viral infections such as AIDS, neurodegenerative disorders, osteoporosis.

### 25 Proteins of SEQ ID NOs: 174, 175 and 232

The proteins of SEQ ID NOs: 174, 175 and 232 encoded by the extended cDNAs SEQ ID NOs:. 73, 74 and 131 respectively and isolated from lymphocytes shows complete extensive homologies to a human secreted protein (Genseq accession number W36955, SEQ ID NO: 517). As shown by the alignments of figure 11, the amino acid residues are identical to those of the 110 amino acid long matched protein except for positions 51 and 108-110 of the matched protein for the protein of SEQ ID NOs: 174, for positions 48, 94 and 108-110 of the matched protein of SEQ ID NOs: 175 and for positions 94, and 108-110 of the matched protein for the protein of SEQ ID NOs: 232. Proteins of SEQ ID NOs: 174 and 232 may represent alternative forms issued from alternative use of polyadenylation signals.

Taken together, these data suggest that the proteins of SEO ID NOs: 174, 175 and 232 may play a role in cell proliferation and/or differentiation, in immune responses and/or in haematopoeisis. Thus, this protein or part therein,



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may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents and/or to suppress graft rejection.

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### Proteins of SEQ ID NO: 231

The protein of SEQ ID NO: 231 encoded by the extended cDNA SEQ ID NO: 130 shows extensive homology with the human E25 protein (Genbank accession number AF038953, SEQ ID NO: 515). As shown by the alignments in figure 12, the amino acid residues are identical except for position 159 in the 263 amino acid long matched sequence. The matched protein might be involved in the development and differentiation of haematopoietic stem/progenitor cells.

In addition, it is the human homologue of a murine protein thought to be involved in chondro-osteogenic differentiation and belonging to a novel multigene family of integral membrane proteins (Deleersnijder et al, J. Biol. Chem., 271: 19475-19482 (1996)).

The protein of invention contains two short segments from positions 1 to 21 and from 100 to 120 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10 : 685-686 (1994)). The first transmembrane domains matches exactly those predicted for the murine E25 protein.

Taken together, these data suggest that the protein of SEO ID NO: 231 may be involved in cellular proliferation and differentiation. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer and embryogenesis disorders.

### 20 Protein of SEQ ID NO: 196

The protein of SEQ ID NO: 196 encoded by the extended cDNA SEQ ID NO: 95 shows extensive homology with the human seventransmembrane protein (Genbank accession number Y11395, SEQ ID NO: 518) and its murine homologue (Genbank accession number Y11550). As shown by the alignments in figure 13, the amino acid residues are identical except for position 174 in the 399 amino acid long human matched sequence. The matched protein potentially associated to stomatin may act as a G-protein coupled receptor and is likely to be important for the signal transduction in neurons and haematopoietic cells (Mayer et al, Biochem. Biophys. Acta., 1395: 301-308 (1998)).

Taken together, these data suggest that the protein of SEO ID NOs: 196 may be involved in signal transduction. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases cardiovascular disorders, hypertension, renal injury and repair and septic 30 shock.

#### Protein of SEQ ID NO: 158

The protein of SEQ ID NOs: 158 encoded by the extended cDNA SEQ ID NO: 57 shows homology with the murine subunit 7a of the COP9 complex (Genbank accession number AF071316, SEQ ID NO: 520). As shown by the

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alignments in figure 14, the amino acid residues are identical except for positions 90, 172 and 247 in the 275 amino acid long matched sequence. This complex is highly conserved between mammals and higher plants where it has been shown to act as a repressor of photomorphogenesis All the components of the mammalian COP9 complex contain structural features also present in components of the proteasome regulatory complex and the translation initiation complex eIF3 complex, suggesting that the mammalian COP9 complex is an important cellular regulator modulating multiple signaling pathways (Wei et al, Curr. Biol., 8 : 919-922 (1998)).

Taken together, these data suggest that the protein of SEQ ID NO: 158 may be involved in cellular signaling, probably as a subunit of the human COP9 complex. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair and septic shock.

### Protein of SEQ ID NO: 226

The protein of SEQ ID NO: 226 encoded by the extended cDNA SEQ ID NO: 125 shows homology with the bovine subunit B14.5B of the NADH-ubiquinone oxidureductase complex (Arizmendi et al, FEBS Lett., 313: 80-84 (1992) and Swissprot accession -number Q02827, SEQ ID NO: 514). As shown by the alignments in figure 15, the amino acid residues are identical except for positions 3-4, 6-12, 32-34, 47, 53-55, 67 and 69-74 in the 120 amino acid long matched sequence. This complex is the first of four complexes located in the inner mitochondrial membrane and composing the mitochondrial electron transport chain. Complex I is involved in the dehydrogenation of NADH and the transportation of electrons to coenzyme Q. It is composed of 7 subunits encoded by the mitochondrial genome and 34 subunits encoded by the nuclear genome. It is also thought to play a role in the regulation of apoptosis and necrosis. Mitochondriocytopathies due to complex I deficiency are frequently encountered and affect tissues with a high energy demand such as brain (mental retardation, convulsions, movement disorders), heart (cardiomyopathy, conduction disorders), kidney (Fanconi syndrome), skeletal muscle (exercise intolerance, muscle weakness, hypotonia) and/or eye (opthmaloplegia, ptosis, cataract and retinopathy). For a review on complex I see Smeitink et al., Hum. Mol. Gent., 7: 1573-1579 (1998).

Taken together, these data suggest that the protein of SEQ ID NO: 226 may be part of the mitochondrial energy-generating system, probably as a subunit of the NADH-ubiquinone oxidoreductase complex. Thus, this protein or part therein, may be useful in diagnosing and/or treating several disorders including, but not limited to, brain disorders (mental retardation, convulsions, movement disorders), 'heart disorders (cardiomyopathy, conduction disorders), kidney disorders (Fanconi syndrome), skeletal muscle disorders (exercise intolerance, muscle weakness, hypotonia) and/or eye disorders opthmalmoplegia, ptosis, cataract and retinopathy).

B) Proteins which are remotely related to proteins with known functions

Proteins of SEQ ID NOs: 149, 150 and 211





The proteins of SEQ ID NOs: 1.49,150 and 211 encoded by the extended cDNAs SEQ ID NOs: 48, 49 and 110 respectively and found in, skeletal muscle shows homologies with T1/ST2 ligand polypeptide of either human (Genbank accession number U41804 and Genseq accession number W09639) or rodent species (Genbank accession number U41805 and Genseq accession number W09640). These polypeptides are thought to be cytokines that bind to the ST2 receptor, a member of the immunoglobulin family homologous to the interleukin-1 receptor and present on some lymphoma cells. They are predicted to be cell-surface proteins containing a short transmembrane domain. (Gayle et al, J. Biol. Chem., 271: 5784-5789 (1996)). Proteins of SEQ ID NOs: 149, 150 and 211 may represent alternative forms issued from alternative use of polyadenylation signals.

The protein of invention contains two short transmembrane segments from positions 5 to 25 and from 195 to 215 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, **10**:685-686 (1994)). The second transmembrane domain matches exactly those of the matched cell-surface protein.

Taken together, these data suggest that the protein of SEQ ID NOs: 149, 150 and 211 may act as a cytokine, thus may play a role in the regulation of cell growth and differentiation and/or in the regulation of the immune response. Thus, this protein or part therein, may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents such as HIV and/or to suppress graft rejection.

### Protein of SEQ ID NO: 177

The protein SEQ ID NO: 177 found in testis encoded by the extended cDNA SEQ ID NO: 76 shows homologies to serine protease inhibitor proteins belonging to the pancreatic trypsin inhibitor family (Kunitz) such as the extracellular proteinase inhibitor named chelonianin (Swissprot accession number P00993). The characteristic PROSITE signature of this family is conserved in the protein of the invention (positions 69 to 87) except for a drastic change of the last cysteine residue into an arginine residue.

Taken together, these data suggest that the protein of SEQ ID NO: 177 may be a protease inhibitor, probably
of the Kunitz family. Thus, this protein or part therein, may be useful in diagnosing and treating several disorders including but not limited to, cancer and neurodegenerative disorders such as Alzheimer's disease.

### Protein of SEQ ID NO: 146

The protein SEQ ID NO: 146 encoded by the extended cDNA SEQ ID NO: 45 shows homology to human apolipoprotein L (Genbank accession number AFO19225). The matched protein is a secreted high density lipoprotein associated with apoA-l-containing lipoproteins which play a key role in reverse cholesterol transport.

Taken together, these data suggest that the protein of SEQ ID NO. 146 may play a role in lipid metabolism. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to,





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hyperlipidemia, hypercholesterolemia, atherosclerosis, cardiovascular disorders such as, coronary heart disease, and neurodegenerative disorders such as Alzheimer's disease or dementia.

#### Protein of SEQ ID NO: 163

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The protein SEQ ED NO: 163 encoded by the extended cDNA SEQ ID NO: 62 shows homology to the yeast autophagocytosis protein AUT1 (SwissProt accession number P40344). The matched protein is required for starvation-induced non-specific bulk transport of cytoplasmic proteins to the vacuole.

Taken together, these data suggest that the protein of SEQ ID NO: 163 may play a role in protein transport.

Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to,
autoimmune disorders and immune disorders due to dysfunction of antigen presentation.

## C) Proteins homologous to a domain of a protein with known function

#### Protein of SEQ ID NO: 214

The protein of SEQ ID NO: 214 encoded by the extended cDNA SEQ ID NO: 113 and expressed in adult brain shows extensive homology to part of the murine SHYC protein (Genbank accession number AF072697) which is expressed in the developing and embryonic nervous system as well as along the olfactory pathway in adult brains (Köster et al., Neuroscience Letters., 252: 69-71 (1998)).

Taken together, these data suggest that the protein of SEQ ID NO: 214 may play a role in nervous system development and function. Thus, this protein may be useful in diagnosing and/or treating cancer and/or brain disorders, including neurodegenerative disorders such as Alzheimer's and Parkinson's diseases.

### Protein of SEQ ID NO: 225

The protein of SEQ ID NO: 225 encoded by the extended cDNA SEQ ID NO: 124 and expressed in adult prostate belong to the phosphatidylethanolainin-binding protein from which it exhibits the characteristic PROSITE signature from positions 90 to 112 (see table VIII). Proteins from this widespread family, from nematodes to fly, yeast, rodent and primate species, bind hydrophobic ligands such as phospholipids and nucleotides. They are mostly expressed in brain and in testis and are thought to play a role in cell growth and/or maturation, in regulation of the sperm maturation, motility and 'in membrane remodeling. They may act either through signal transduction or through oxidoreduction reactions (for a review see Schoentgen and Jollès, FEBS Letters, 369 : 22-26 (1995)).

Taken together, these data suggest that the protein of SEQ ID NO: 225 may play a role in cell. Thus, these growth, maturation and in membrane remodeling and/or may be related to male fertility. Thus, this protein may be useful in diagnosing and/or treating cancer, neurodegenerative diseases, and/of, disorders related to male fertility and sterility.

#### Protein of SEO ID NO: 153



The protein of SEQ ID NO: 153 encoded by the extended cDNA SEQ ID NO. 52 and expressed in brain exhibits homology to different integral membrane proteins. These membrane proteins include the nematode protein SRE-2 (Swissprot accession number 009273) that belongs to the multigene SRE family of *C. elegans* receptor-like proteins and a family of tricarboxylate carriers conserved between flies and mammals. One member of this matched family is the rat 5 tricarboxylate carrier (Genbank accession number S70011), an anion transporter localized in the inner membrane of mitochondria and involved in the biosynthesis of fatty acids and cholesterol. The protein of the invention contains a short transmembrane segments from positions 5 to 25 as predicted by the software TopPred II (Claros and von Heijne, CABIOS applic. Notes, 10:685-686 (1994)).

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Taken together, these data suggest that the protein of SEQ ID NO: 153 may play a role in signal transduction 10 and/or in molecule transport. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, immune disorders, cardiovascular disorders, hypertension, renal injury and repair and septic shock

### Protein of SEQ ID NO: 213

The protein of SEQ ID NO: 213 encoded by the extended cDNA SEQ ID NO: 112 and expressed in brain exhibits 15 homology with part of the tRNA pseudouridine 55 synthase found in Escherichia Coli (Swissprot accession number P09171). This bacterial protein belongs to the NAP57/CBF5/TRUB family of nucleolar proteins found in bacteria, yeasts and mammals involved in rRNA or tRNA biosynthesis, ribosomal subunit assembly and/or centromere/mircotubule binding.

Taken together, these data suggest that the protein of SEQ ID NO: 213 may play a role in rRNA or tRNA biogensis and function. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, hearing loss or disorders linked to chromosomal instability such as dyskeratosis.

### Protein of SEQ ED NO: 240

The protein of SEQ ID NO: 240 encoded by the extended cDNA SEQ ID NO: 139 and expressed in brain exhibits homology with a family of eukaryotic cell surface antigens containing 4 transmembrane domains. The PROSITE signature for this family is conserved in the protein of the invention except for a substitution of an alanine residue in place of any of the following hydrophic residues: leucine, valine, isoleucine or methionine (positions 21 to 36).

The protein of the invention contains three short transmembrane segments from positions 6 to 26, 32 to 52 30 and from 56 to 76 as predicted by the software TopPred II (Claros and von Heijne, CABIOS applic. Notes, 10: 685-686 (1994)). These transmembrane domains match the last three transmembrane domains of the matched protein family.

Taken together, these data suggest that the protein of SEQ ID NO: 240 may play a role in immunological and/or inflammatory responses, probably as a cell surface antigen. Thus, this protein or part therein, may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or

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inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents and/or to suppress graft rejection.

#### Protein of SEQ ID NO: 239

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The protein of SEQ ID NO: 239 encoded by the extended cDNA SEQ ID NO: 138 exhibits homology with a conserved region in a family of NA+/H+ exchanger conserved in yeast, nematode and mammals. These cation/proton exchangers are integral membrane proteins with 5 transmembrane segments involved in intracellular pH regulation, maintenance of cell volume, reabsorption of sodium across specialized epithelia, vectorial transport and are also thought to play a role in signal transduction and especially in the induction of cell proliferation and in the induction of apoptosis.

The protein of invention contains four short transmembrane segments from positions 21 to 41, 48 to 68 and from 131 to 151 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10: 685-686 (1994)). The third and fourth transmembrane domains match the fourth and fifth transmembrane segments of the matched family of proteins.

Taken together, these data suggest that the protein of SEQ ID NO: 239 may play a role in membrane

15 permeability and/or in signal transduction. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair, septic shock as well as disorders of membrane permeability such as diarrhea.

#### Protein of SEQ ID NO: 200

The protein of SEQ ID NO: 200 encoded by the extended cDNA SEQ ED NO: 99 and expressed in brain exhibits extensive homology to the N-terminus of cell division cycle protein 23 (Genbank accession number AF053977) and also to a lesser extent to its homologue in *Saccharomyces cerevisiae*. The matched protein is required for chromosome segregation and is part of the anaphae-promoting complex necessary for cell cycle progression to mitosis.

Taken together, these data suggest that the protein of SEQ ID NO: 200 may play a role in cellular mitosis.

Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer and leukemia.

#### Protein of SEQ ID NO: 230

The protein of SEQ ID NO: 230 encoded by the extended cDNA SEQ ID NO: 129 exhibits extensive homology to the C-terminus of the eta subunit of T-complex polypeptide 1 conserved from yeasts to mammals, and even complete identity with the last 54 amino acid residues of the human protein (Genbank accession number AF026292). The matched protein is a chaperonin which assists the folding of actins and tubulins in eukaryotic cells upon ATP hydrolysis.

Taken together, these data suggest that the protein of SEQ ID NO: 230 may play a role in the folding, transport, assembly and degradation of proteins. Thus, this protein may be useful in diagnosing and/or treating several



types of disorders including, but not limited to, cancer, cardiovascular disorders, immune disorders, neurodegenerative disorders, osteoporosis and arthritis.

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### Protein of SEQ ED NO: 167

The protein of SEQ ID NO: 167 encoded by the extended cDNA SEQ ID NO: 66 exhibits homology to a monkey pepsinogen A-4 precursor (Swissprot accession number P27678) and to related members of the aspartyl protease family. The matched protein belongs to a family of widely distributed proteolytic enzymes known to exist in vertebrate, fungi, plants, retroviruses and some plant viruses.

Taken together, these data suggest that the protein of SEQ ID NO: 167 may play a role in the degradation of proteins. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, autoimmune disorders and immune disorders due to dysfunction of antigen presentation.

### Protein of SEQ ID NO: 179

The protein of SEQ ID NO: 179 encoded by the extended cDNA SEQ ID NO: 78 found in testis exhibits

homology to part of mammalian colipase precursors. Colipases are secreted cofactors for pancreatic lipases that allow the lipase to anchor at the water-lipid interface. Colipase plays a crucial role in the intestinal digestion and absorption of dietary fats. The 5 cysteines characteristic for this protein family are conserved in the protein of the invention although the colipase PROSITE signature is not.

Taken together, these data suggest that the protein of SEQ ED NO: 179 may play a role in the lipid metabolism and/or in male fertility. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, hyperlipidemia, hypercholesterolemia, atherosclerosis, cardiovascular disorders such as coronary heart disease, and neurodegenerative disorders such as Alzheimer's disease or dementia, and disorders linked to male fertility.

### 25 Protein of SEQ ID NO: 227

The protein of SEQ ID NO: 227 encoded by the extended cDNA SEQ ID NO: 126 exhibits extensive homology to the ATP binding region of a whole family of serine/threonine protein kinases belonging to the CDC2/CDC28 subfamily. The PROSITE signature characteristic for this domain is present in the protein of the invention from positions 10 to 34.

Taken together, these data suggest that the protein of SEQ ED NO: 158 may bind ATP, and even be a protein solution with the protein of SEQ ED NO: 158 may bind ATP, and even be a protein the second several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair and septic shock.

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Although this invention has been described in terms of certain preferred embodiments, other embodiments which will be apparent to those of ordinary skill in the art in view of the disclosure herein are also within the scope of this invention. Accordingly, the scope of the invention is intended to be defined only by reference to the appended claims.

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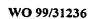
As discussed above, the extended cDNAs of the present invention or portions thereof can be used for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to 10 compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination for expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins or polypeptides provided by the present invention can similarly be used in assays to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine 😘 levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other 25 protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning; A Laboratory Manual", 2d ed., Cole Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology; Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a





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nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

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### SEQUENCE LISTING FREE TEXT

The following free text appears in the accompanying Sequence Listing:

In vitro transcription product

oligonucleotide

5 promoter

transcription start site

Von Heijne matrix

Score

matinspector prediction

10 name

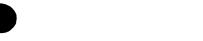




### TABLE !

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SEQ ID NO. in	Provisional Application Disclosing Sequence	050 10 110 :
Present applicatio	n	SEQ ID NO. in provisional application
40	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	51
41	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	72
42	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	52
43	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	78
44	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	73
45	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	41
46	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	67
47	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	82
48	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	<del></del>
49	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	80
50	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	81
51	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	53
52	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	54
53	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	195
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55	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	46
56	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	68
57	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	48
58	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	55
	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	49
59	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	50
60	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	97
62	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	51
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271	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	104
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273	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	106
274	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	107
275	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	108
276	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	109
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278	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	111
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287	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	120
288	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	121
289	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	122
290	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	123
291	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	124
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293	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	126
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367	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	200
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369	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	202
370	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	203
371	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	203
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373	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	205
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TABLE II : Parameters used for each step of EST analysis

		Search Charac	teristics	Selection Charac	teristics
Step	Program	Strand	Parameters	Identity (%))	Length (bp)
Miscellaneous	Blastn	both	S-61 X-16	90	17
tRNA	Fasta	both	•	80	60
rRNA	Blastn	both	S=108	80	40
mtRNA	Blastn	both	S-108	80	40
Procaryotic	Blastn	both	S=144	90	40
Fungal	Blastn	both	S=144	90	40
Alu	fasta*	both	•	70	40
L1	Blastn	both	S-72	70	40
Repeats	Biastn	both	S=72	70	40
Promoters	Blastn	top	S-54 X-16	90	15⊥
Vertebrate	fasta*	both	S-108	90	30
ESTs	Blatsn	both	S-108 X-16	90	30
Proteins	blastxŋ	top	E-0.001		

<sup>\*</sup> use "Quick Fast" Database Scanner

 $<sup>\</sup>perp\,$  alignment further constrained to begin closer than 10bp to EST\5' end

 $<sup>5 \</sup>quad \eta \quad \text{using BLOSUM62 substitution matrix}$ 

Vertebrate\*

ESTs\*

ORF

Geneseq

Proteins\*

**BLASTN** then

**FASTA** 

BLAST2N

BLASTN

BLASTP

BLASTX

preceding the 5' end of the

first BLASTN and then

on ORF proteins, max 10

FASTA on matching sequences

polA

matches





TABLE III: Parameters used for each step of extended cDNA analysis

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Search characteristics Selection characteristics Step Program Strand **Parameters** Identity (%) Length (bp) Comments miscellaneous **FASTA** both 90 15 tRNA\* FASTA both 80 90 rRNA\* BLASTN both S-108 80 40 mtRNA\* BLASTN both S-108 80 40 Procaryotic<sup>1</sup> BLASTN both S-144 90 40 Fungal\* BLASTN both S-144 90 40 Alu\* BLASTN both S-72 70 40 max 5 matches, masking L1<sup>\*</sup> BLASTN both S-72 70 40 max 5 matches, masking Repeats\* BLASTN S-72 both 70 40 masking PolyA BLAST2N top W-6,S-10,E-1000 8 in the last 20 nucleotides Polyadenylati AATAAA allowing 1 mismatch top in the 50 nucleotides on signal

90 then 70

90

90

70

30

30

30

30

both

both

both

top

top

W-8, B-10

W-8, B-10

E-0.001

steps common to EST analysis and using the same algorithms and parameters

<sup>5 \*</sup> steps also used in EST analysis but with different algorithms and/or parameters



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## TABLE IV

Id	FCS Location	SigPep Location	Polypeptide	Stop Codon	PolyA Signal Location	PolyA Site Location
40	7 through 471	7 through 99	Location 100 through 471	Location 472		
41	168 through 332		168 through 332	333	537 through 542	554 through 568
42	51 through 251	51 through 110	111 through 251		557 through 562	
43	20 through 613	20 through 82	83 through 613	252 614	849 through 854	882 through 895
44	12 through 416	12 through 86	87 through 416		1.	•
45	276 through 1040	i_	486 through 1040	417	425 through 430	445 through 458
46	443 through 619	443 through 589	590 through 619		·	2024 through 2036
47	206 through 747	440 tinough 309	<u> </u>	620	•	1267 through 1276
48	36 through 521	36 through 104	206 through 747		·	•
49	36 through 395	36 through 104	105 through 521	522	528 through 533	548 through 561
50	21 through 41	30 through 104	105 through 395	396	599 through 604	619 through 632
51	35 through 631	25 41	21 through 41	42	328 through 333	357 through 370
52	271 through 399	35 through 160	161 through 631	632	901 through 906	979 through 994
53		100 1 100	271 through 399	400	•	
54	103 through 252	103 through 213	214 through 252	253	•	588 through 597
55	2 through 460	·	2 through 460	461	713 through 718	735 through 748
	31 through 231	·	31 through 231	232	769 through 774	690 through 703
56	305 through 565		305 through 565	566	694 through 699	713 through 725
57	124 through 873	124 through 378	379 through 873	874	1673 through 1678	1694 through 1705
58	135 through 206		135 through 206	207	850 through 855	1056 through 1069
59	135 through 818		135 through 818	819	909 through 914	1071 through 1084
60	33 through 290	33 through 92	93 through 290	291	·	1.
61	485 through 616	•	485 through 616	617	·	669 through 682
62	54 through 995	54 through 227	228 through 995	996	1130 through 1135	1181 through 1191
63	657 through 923	657 through 896	897 through 923	924	957 through 962	974 through 1008
64	18 through 311	18 through 62	63 through 311	312		1.
65	151 through 426	151 through 258	259 through 426	427	505 through 510	527 through 538
<b>6</b> 6	10 through 1062	10 through 57	58 through 1062	1063	1710 through 1715	1735 through 1747
67	78 through 491	78 through 218	219 through 491	492	1652 through 1657	1673 through 1686
68	69 through 371	69 through 287	288 through 371	372	510 through 515	530 through 542
69	2 through 757	2 through 205	206 through 757	758		1160 through 1174
70	2 through 1051	2 through 205	206 through 1051	1052	1248 through 1253	1272 through 1285
71	2 through 1171	2 through 205	206 through 1171	1172	1368 through 1373	1386 through 1398
72	42 through 611	42 through 287	288 through 611	612	787 through 792	808 through 821
73	62 through 916	62 through 757	758 through 916	-		904 through 916
74	62 through 520	•	62 through 520	521	1124 through 1129	1141 through 1153
75	21 through 167	•	21 through 167	168		·
76	22 through 318	22 through 93	94 through 318	319	497 through 502	516 through 526
77	8 through 292	8 through 118	119 through 292	293	317 through 322	339 through 352
78	16 through 378			379	502 through 507	522 through 542





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### CONT. TABLE IV

_ 00	NT. TABLE IV					
79	57 through 233	·	57 through 233	1.		·
80	83 through 340	83 through 124	125 through 340	341	573 through 578	607 through 660
81	47 through 541	47 through 220	221 through 541	542		597 through 605
82	46 through 285	46 through 150	151 through 285	286	364 through 369	385 through 396
83	22 through 240	22 through 84	85 through 240	241	397 through 402	421 through 432
84	89 through 382		89 through 382	383		421 through 432
85	80-through 415	80 through 142	143 through 415	416	471 through 476	
86	152 through 361	152 through 283		362	471 tinough 470	488 through 501
87	32 through 307	32 through 70	71 through 307	308	1240 through 1245	1201 11 1 107
88	114 through 734	114 through 239		735	768 through 773	1261 through 127
89	199 through 802		199 through 802	1.		793 through 804
90	38 through 1174	38 through 148	149 through 1174		780 through 785	791 through 802
91	26 through 361		26 through 361	1175	1452 through 1457	1478 through 1490
92	3 through 131		3 through 131		•	350 through 361
93	33 through 185	33 through 80	81 through 185	132		591 through 605
94	184 through 915	184 through 237	<u>-</u>	186	570 through 575	586 through 591
95	58 through 1116		238 through 915	916	1119 through 1124	1139 through 1150
96	327 through 417	58 through 159	160 through 1116	1117	1486 through 1491	1504 through 1513
97	63 through 398	F2 41 . 1 . 000	327 through 417	· .	•	404 through 417
98		63 through 206	207 through 398	399	·	-
99	2 through 163	1.	2 through 163	164	488 through 493	511 through 522
100	13 through 465	13 through 75	76 through 465	466	•	•
	20 through 703	20 through 94	95 through 703	704	1000 through 1005	1023 through 1041
101	103 through 294	103 through 243	244 through 294	295		1.
02	81 through 518	81 through 173	174 through 518	519	-	·
03	66 through 326	<u> </u>	66 through 326	327	1066 through 1071	1087 through 1098
04	170 through 289	170 through 250	251 through 289	290	•	
05	36 through 497		36 through 497	498	650 through 655	663 through 685
06	18 through 320	·	18 through 320	321	539 through 544	542 through 554
07	71 through 1438	71 through 136	137 through 1438	1439	1644 through 1649	1665 through 1678
80	25 through 318	25 through 75	76 through 318	319	452 through 457	482 through 494
09	84 through 332	84 through 170	171 through 332	333		702 through 714
10	32 through 718	32 through 100	101 through 718	719	770 through 775	793 through 805
1	26 through 481	26 through 88	89 through 481	482	755 through 760	775 through 787
	26 through 562	26 through 187	188 through 562	563	1.	
3	4 through 810	4 through 279	280 through 810	811	858 through 863	881 through 893
4	55 through 459	55 through 120	121 through 459	460	1444 through 1449	1462 through 1475
5	48 through 248	48 through 161	162 through 248	249	283 through 288	308 through 321
6	25 through 399	25 through 186	187 through 399	400		
7	10 through 1137	10 through 72	73 through 1137	1138	1144 through 1149	
8	72 through 704		162 through 704	705	772 through 777	1162 through 1173
·   '					, , _ cu. uuyu / / /	•
	44 through 505	44 through 223	224 through 505	506		





#### CONT. TARLE IV

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122	31 through 660	31 through 90	91 through 660	661	1288 through 1293	1307 through 1318
123	31 through 582	31 through 90	91 through 582	583	816 through 821	840 through 853
124	15 through 695	15 through 80	81 through 695	696	795 through 800	814 through 826
125	74 through 295	74 through 196	197 through 295	296	545 through 550	561 through 571
126	440 through 659	-	440 through 659	1.	601 through 606	
127	38 through 283	38 through 85	86 through 283	284	257 through 262	1.
128	121 through 477	121 through 288	289 through 477	1.		
129	2 through 163		2 through 163	164	292 through 297	310 through 323
130	46 through 675	46 through 87	88 through 675	676	1364 through 1369	1383 through 1392
131	62.through 385	•	62 through 385	386	974 through 979	987 through 999
132	422 through 550	422 through 475	476 through 550	551		714 through 725
133	124 through 231	·	124 through 231	232	1.	387 through 400
134	131 through 1053	131 through 169	170 through 1053		1019 through 1024	<del>                                     </del>
135	86 through 403	86 through 181	182 through 403	404	1097 through 1102	1117 through 1128
136	37 through 162	37 through 93	94 through 162	163	224 through 229 .	243 through 254
137	31 through 381	31 through 90	91 through 381	382		875 through 886
138	46 through 579	46 through 156	157 through 579	580	•	
139	92 through 471	92 through 172	173 through 471	· -	454 through 459	458 through 471
140	154 through 675	154 through 498	499 through 675	676	819 through 824	838 through 849
242	18 through 173	18 through 77	78 through 173	174	864 through 869	882 through 893
243	17 through 595	17 through 85	86 through 595	596	820 through 825	840 through 851
244	89 through 334	89 through 130	131 through 334	335	462 through 467	484 through 495
245	21 through 614	21 through 83	84 through 614	615	849 through 854	873 through 884
246	94 through 573	94 through 258	259 through 573	574	862 through 867	886 through 897
247	74 through 397	74 through 127	128 through 397	398	472 through 477	507 through 518
248	51 through 242	51 through 116	117 through 242	243	319 through 324	339 through 350
249	111 through 191	111 through 155	156 through 191	192	965 through 970	986 through 996
250	45 through 602	45 through 107	108 through 602	603	828 through 833	850 through 860
251	24 through 560	24 through 101	102 through 560	561	563 through 568	583 through 593
252	109 through 558	109 through 273	274 through 558	559	•	1104 through 1114
253	128 through 835	128 through 220	221 through 835	836	1145 through 1150	1170 through 1181
254	59 through 505	59 through 358	359 through 505	506	1042 through 1047	1062 through 1073
255	1 through 207	1 through 147	148 through 207	208	784 through 789	807 through 818
256	12 through 734	12 through 101	102 through 734	.735	914 through 919	961 through 971
257	378 through 518	378 through 467	468 through 518	519	607 through 612	628 through 640
258	110 through 304	110 through 193	194 through 304	305	708 through 713	732 through 743
259	201 through 419	201 through 272	273 through 419	420	601 through 606	627 through 637
260	123 through 302	123 through 176	177 through 302	303	1279 through 1284	1301 through 1312
261	98 through 673	98 through 376	377 through 673	674		1025 through 1035
262	17 through 463	17 through 232	233 through 463	464	657 through 662	684 through 696
263	263 through 481	263 through 322	323 through 481	482		858 through 868
		<del></del>			L	

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668 through 681



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C	ONT. TABLE IV			-112-		
26		42 through 101	102 through 299	300		762 through 775
26	5 198 through 43	1 198 through 260	261 through 431	432	<del></del>	
26	6 279 through 47	3 279 through 362	2 363 through 473		944 through 949	970 through 981
26	7 12 through 644	12 through 92	93 through 644	645	1002 through 1007	
26	8 91 through 459	91 through 330	331 through 459		1002 till dagil 1007	
26	9 70 through 327	70 through 147	148 through 327		1741 through 1746	1271 through 1281
270	12 through 497	12 through 104	105 through 497	498	935 through 940	
271	90 through 383	90 through 200	201 through 383	384	609 through 614	955 through 967
272	332 through 541	332 through 376		542	739 through 744	632 through 643
273	43 through 222	43 through 177	178 through 222	223	530 through 535	761 through 773
274	115 through 231	115 through 180	181 through 231	232	419 through 424	555 through 566
275	232 through 384	232 through 300	301 through 384	385		445 through 455
276	143 through 427		287 through 427	428	650 through 655	662 through 673
277	284 through 463	294 through 379	380 through 463	464	606 through 611	628 through 639
278	162 through 671	162 through 398	399 through 671	672		762 through 772
279	63 through 632	63 through 308	309 through 632		805 through 810	830 through 840
280	21 through 362	21 through 200	201 through 362	633	808 through 813	829 through 840
281	21 through 503	21 through 344	345 through 503	363	821 through 826	838 through 849
282	1 through 201	1 through 63	64 through 201	504	1305 through 1310	1330 through 1341
283	39 through 1034	39 through 134	135 through 1034	202	637 through 642	660 through 671
284	69 through 263	69 through 125		1035	1566 through 1571	1587 through 1597
285	115 through 285	115 through 204	126 through 263	264	1173 through 1178	1196 through 1205
286	90 through 344	90 through 140	205 through 285	286	505 through 510	525 through 536
287	57 through 311	57 through 107	141 through 344	345	500 through 505	515 through 527
288	96 through 302	96 through 182	108 through 311	312	467 through 472	482 through 493
289	161 through 526	161 through 328	183 through 302	303	•	501 through 514
290	210 through 332		329 through 526	527		799 through 811
291	212 through 361	210 through 299	300 through 332	333	594 through 599	613 through 625
292	75 through 482	212 through 319	320 through 361	362	650 through 655	673 through 684
293	50 through 631	75 through 128	129 through 482	483	595 through 600	618 through 627
294	154 through 576	50 through 244	245 through 631	632	777 through 782	801 through 812
295		154 through 360	361 through 576	577	737 through 742	763 through 775
296	154 through 897 146 through 292	154 through 360	361 through 897	898	1017 through 1022	1044 through 1054
297		146 through 253	254 through 292	293	395 through 400	433 through 444
298	126 through 383	126 through 167	168 through 383 .	384	726 through 731	743 through 754
299	66 through 497		240 through 497	498	594 through 599	618 through 629
	49 through 411		97 through 411	412	732 through 737	750 through 763
300	49 through 534		97 through 534	535	593 through 598	612 through 623
301	86 through 415		146 through 415	416	540 through 545	560 through 571
302	56 through 268		101 through 268	269	584 through 589	601 through 612
	32 through 328		104 through 328	329	508 through 513	528 through 539
	21 through 527		36 through 527	528	921 through 926	953 through 963
305	147 through 647	147 through 374 3	375 through 647	648		668 through 681

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# CONT. TABLE IV

	JNT. TABLE IV					•	
30			307 through 471	472	663 through 668	682 through 693	_
30		74 through 172	173 through 1216	3 1217	1627 through 1632	1640 through 1652	_
30		48 through 89	90 through 164	165	482 through 487	505 through 517	_
30			296 through 334	335	355 through 360	392 through 405	_
311		195 through 272	273 through 347	348	1037 through 1042	1071 through 1082	
31		90 through 179	180 through 815	816	883 through 888	905 through 916	-
312		52 through 231	232 through 513	514	553 through 558	572 through 583	_
313		172 through 354	355 through 438	439	682 through 687	685 through 697	_
314		148 through 225	226 through 366	367	770 through 775	792 through 803	_
315		175 through 276	277 through 336	337		812 through 823	-
316		191 through 304	305 through 553	554	766 through 771	804 through 817	
317	106 through 603	106 through 216	217 through 603	604		1102 through 1112	
318	47 through 586	47 through 124	125 through 586	587	1583 through 1588	1614 through 1623	_
319	99 through 371	99 through 290	291 through 371	372	491 through 496	513 through 524	-
320	44 through 814	44 through 112	113 through 814	815	· · · · · · · · · · · · · · · · · · ·	978 through 989	$\dashv$
321	3 through 581	3 through 182	183 through 581	582	1.	1006 through 1016	┥
322	107 through 427	107 through 190	191 through 427	428	499 through 504	516 through 529	┥
323	45 through 407	45 through 83	84 through 407	408	1008 through 1013	1032 through 1042	$\dashv$
324	201 through 332	201 through 251	252 through 332	333		869 through 880	$\dashv$
325	217 through 543	217 through 255	256 through 543	544	<del> </del> -	1206 through 1217	$\dashv$
326	18 through 446	18 through 140	141 through 446	447	930 through 935	948 through 959	$\dashv$
327	29 through 724	29 through 118	119 through 724	725	886 through 891	910 through 920	+
328	404 through 586	404 through 466	467 through 586	587	1304 through 1309	1334 through 1344	-
329	331 through 432	331 through 387	388 through 432	433	548 through 553	573 through 585	$\frac{1}{2}$
330	59 through 703	59 through 220	221 through 703	704	886 through 891	903 through 914	$\frac{1}{1}$
331	672 through 752	672 through 722	723 through 752	753		1150 through 1161	+
332	57 through 311	57 through 128	129 through 311	312	332 through 337	351 through 363	}
333	80 through 232	80 through 127	128 through 232	233	617 through 622	634 through 645	}
334	91 through 291	91 through 219	220 through 291	292	367 through 372	389 through 400	1
335	196 through 384	196 through 240	241 through 384	385	461 through 466	485 through 496	
336	54 through 590	54 through 227	228 through 590	591		955 through 965	ĺ
337	133 through 846	133 through 345	346 through 846	847	<del> </del>	890 through 901	
338	138 through 671	138 through 248	249 through 671	672	1319 through 1324	1338 through 1347	
339	124 through 411	124 through 186	187 through 411	412	948 through 953	971 through 983	
340	372 through 494	372 through 443	444 through 494	495	708 through 713	732 through 745	
341	112 through 450	112 through 192	193 through 450	451	1053 through 1058	1095 through 1106	
342	117 through 866	117 through 170	171 through 866	867	1159 through 1164	1178 through 1190	
343	13 through 465	13 through 75	76 through 465	466	1035 through 1040	1060 through 1070	
344	2 through 718	2 through 76	77 through 718	719	1170 through 1175	1203 through 1213	
345	86 through 709		362 through 709	710	943 through 948	963 through 973	
346	63 through 320		180 through 320	321	771 through 776	799 through 810	
347	299 through 418		380 through 418	419	739 through 744	762 through 771	
	·1		•			. oz mougn //!	





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## CONT. TABLE IV

		DIATE INDEE IN					
	34	8 186 through 38	186 through 23:	3   234 through 380	381	383 through 388	200 (1 ) (20
	34	9 <b>69</b> through 458	69 through 233	234 through 458			396 through 409
	35	0 12 through 638	12 through 263	264 through 638		564 through 569	602 through 613
	35	1 282 through 389	282 through 332	I	390	951 through 956	975 through 985
	352	2   208 through 339				1413 through 1418	1437 through 1447
	353	69 through 557	69 through 224	225 through 557	340	·	1631 through 1641
i	354	134 through 325			558	849 through 854	870 through 883
ı	355		78 through 227		326	·	718 through 729
ł	356			228 through 731	732	·	1002 through 1013
-	357		46 through 90	91 through 693	694	937 through 942	962 through 973
+	358		126 through 182	183 through 527	528	834 through 839	856 through 867
ŀ	359		66 through 113	114 through 320	321	490 through 495	508 through 519
-		73 through 948	73 through 159	160 through 948	949	•	1016 through 1028
ŀ	360	69 through 434	69 through 236	237 through 434	435	419 through 424	441 through 452
-	361	628 through 804	628 through 711	712 through 804	805	1.	864 through 875
$\perp$	362	70 through 366	70 through 108	109 through 366	367	496 through 501	521 through 531
-	363	70 through 366	70 through 108	109 through 366	367		1233 through 1244
L	364	111 through 434	111 through 185	186 through 434	435	<del> </del>	618 through 631
<u> </u>	365	19 through 567	19 through 63	64 through 567	568	749 through 754	771 through 781
Ŀ	366	19 through 312	19 through 63	64 through 312	313	896 through 901	<del></del>
3	367	64 through 612	64 through 234	235 through 612	613		921 through 931
63	368	39 through 458	39 through 80	81 through 458	459	613 through 618	839 through 849
3	69	9 through 185	9 through 50	51 through 185	186	· ·	633 through 644
3	70	14 through 316	14 through 121	122 through 316	317		906 through 918
3	71	70 through 1092	70 through 234	235 through 1092	1093	442 through 447	458 through 471
3	72	274 through 597	274 through 399	400 through 597	598	1475 through 1480	1493 through 1504
3	73	230 through 469	230 through 307	308 through 469		731 through 736	754 through 765
3	74	72 through 545	72 through 203		470	1004 through 1009	1027 through 1040
37	75	36 through 425	36 through 119	204 through 545	546		1151 through 1162
_	76	155 through 751	455	120 through 425	426	1215 through 1220	1240 through 1250
37		46 through 585		341 through 751	752	912 through 917	937 through 947
_		- Sandagii 000	46 through 120	121 through 585	586	584 through 589	606 through 619

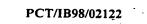


## TABLE V

ld	Full Langeh Dalumani I		
	Full Length Polypeptide Location	Signal Peptide Location	Mature Polypeptide Location
141	-31 through 124	-31 through -1	3 through 104
142	1 through 55	·	1 through 124
143	-20 through 47	-20 through -1	1 through 55 1 through 47
144	-21 through 177	-21 through -1	
145	-25 through 110	-25 through -1	1 through 177
146	-70 through 185	-70 through -1	1 through 110
147	-49 through 10	-49 through -1	1 through 185
148	1 through 180		1 through 10
149	-23 through 139	-23 through -1	1 through 180
150	-23 through 97	-23 through -1	1 through 139
151	1 through 7		1 through 97
152	-42 through 157	-42 through -1	1 through 7
153	1 through 43	· ·	1 through 157
154	-37 through 13	-37 through -1	1 through 43
155	1 through 153	·	1 through 13
156	1 through 67		1 through 153
157	1 through 87		1 through 67
158	-85 through 165	-85 through -1	1 through 87
159	1 through 24	·	1 through 165
160	1 through 228		1 through 24
161	-20 through 66	-20 through -1	1 through 228
162	1 through 44	20 tinuagii - i	1 through 66
163	-58 through 256	-58 through -1	1 through 44
164	-80 through 9	-80 through -1	1 through 256
165	-15 through 83	-15 through -1	1 through 9
166	-36 through 56	-36 through -1	1 through 83
167	-16 through 335	-16 through -1	1 through 56
168	-47 through 91	-47 through -1	1 through 335
169	-73 through 28	-73 through -1	1 through 91
170	-68 through 184	-68 through -1	1 through 28
171	-68 through 282	-68 through -1	1 through 184
172	-68 through 322	-68 through -1	1 through 282
173	-82 through 108	-82 through -1	1 through 322
174	-232 through 53	-232 through -1	1 through 108
175	1 through 153	202 modgn - r	1 through 53
176	1 through 49	-	1 through 153
177	-24 through 75	-24 through -1	1 through 49
178	-37 through 58	-37 through -1	1 through 75
179	-23 through 98	-23 through -1	1 through 58
180	1 through 59	20 through -1	1 through 98
181	-14 through 72	-14 through -1	1 through 59
182	-58 through 107	-58 through -1	1 through 72
183	-35 through 45	-35 through -1	1 through 107
184	-21 through 52	-21 through -1	1 through 45
185	1 through 98	z i tinough · t	1 through 52
186	-21 through 91	-21 through -1	1 through 98
187	-44 through 26	-44 through -1	1 through 91
188	-13 through 79	-13 through -1	1 through 26
189	-42 through 165	-42 through -1	1 through 79
190	1 through 201	-42 (11/bugh -1	1 through 165
			1 through 201







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## CONT. TABLE V

CUNI. TAE	BLE V		
191	-37 through 342	-37 through -1	1 - 1 - 1 - 2 - 2
192	1 through 112	·	1 through 342
193	1 through 43	_	1 through 112
194	-16 through 35	-16 through -1	1 through 43
195	-18 through 226	-18 through -1	1 through 35
196	-34 through 319	-34 through -1	1 through 226
197	1 through 30	-04 (mbugn - )	1 through 319
198	-48 through 64	-48 through -1	1 through 30
199	1 through 54	40 dirbdgit - I	1 through 64
200	-21 through 130	-21 through -1	1 through 54
201	-25 through 203	-21 through -1	1 through 130
202	-47 through 17	-47 through -1	1 through 203
203	-31 through 115		1 through 17
204	1 through 87	-31 through -1	1 through 115
205	-27 through 13	27 through 1	1 through 87
206	1 through 154	-27 through -1	1 through 13
207	1 through 101	<u> </u>	1 through 154
208	-22 through 434	224	1 through 101
209	-17 through 81	-22 through -1	1 through 434
210	-29 through 54	-17 through -1	1 through 81
211	-23 through 206	-29 through -1	1 through 54
212	-21 through 131	-23 through -1	1 through 206
213	-54 through 125	-21 through -1	1 through 131
214	-92 through 177	-54 through -1	1 through 125
215	-22 through 113	-92 through -1	1 through 177
216	-38 through 29	-22 through -1	1 through 113
217	-54 through 71	-38 through -1	1 through 29
218	-21 through 355	-54 through -1	1 through 71
219	-30 through 181	-21 through -1	1 through 355
220	-60 through 94	-30 through -1	1 through 181
221	-42 through 81	-60 through -1	1 through 94
222	-19 through 327	-42 through -1	1 through 81
223	-20 through 190	-19 through -1	1 through 327
224	-20 through 164	-20 through -1	1 through 190
225	-22 through 205	-20 through -1	1 through 164
226	-41 through 33	-22 through -1	1 through 205
227	1 through 73	-41 through -1	1 through 33
228	-16 through 66		1 through 73
229	-56 through 63	-16 through -1	1 through 66
230	1 through 54	-56 through -1	1 through 63
231	-14 through 196		1 through 54
232	1 through 108	-14 through -1	1 through 196
233	-18 through 25		1 through 108
234	1 through 36	-18 through -1	1 through 25
235	-13 through 294	•	1 through 36
236	-32 through 74	-13 through -1	1 through 294
237		32 through -1	1 through 74
238	-19 through 23	-19 through -1	1 through 23
239	-20 through 97	-20 through -1	1 through 97
240	-37 through 141	-37 through -1	1 through 141
241	-27 through 99	-27 through -1	1 through 99
378	-115 through 59	-115 through -1	1 through 59
379	-20 through 32	-20 through -1	1 through 32
	-23 through 170	-23 through -1	
380	-14 through 68	-14 through -1	1 through 170



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## CONT. TABLE V

CONT. TABL	<u>E V                                     </u>		
381	-21 through 177	-21 through -1	1 through 177
382	-55 through 105	-55 through -1	1 through 105
383	-18 through 90	-18 through -1	1 through 90
384	-22 through 42	-22 through -1	1 through 42
385	-15 through 12	-15 through -1	1 through 12
386	-21 through 165	-21 through -1	1 through 165
387	-26 through 153	-26 through -1	1 through 153
388	-55 through 95	-55 through -1	1 through 95
389	-31 through 205	-31 through -1	1 through 205
390	-100 through 49	-100 through -1	1 through 49
391	-49 through 20	-49 through -1	1 through 20
392	-30 through 211	-30 through -1	1 through 211
393	-30 through 17	-30 through -1	1 through 17
394	-28 through 37	-28 through -1	1 through 37
395	-24 through 49	-24 through -1	1 through 49
396	-18 through 42	-18 through -1	1 through 42
397	-93 through 99	-93 through -1	1 through 99
398	-72 through 77	-72 through -1	1 through 77
399	-20 through 53	-20 through -1	1 through 53
400	-20 through 66	-20 through -1	1 through 66
401	-21 through 57	-21 through -1	1 through 57
402	-28 through 37	-28 through -1	1 through 37
403	-27 through 184	-27 through -1	1 through 184
404	-80 through 43	-80 through -1	1 through 43
405	-26 through 60	-26 through -1	1 through 60
406	-31 through 131	-31 through -1	1 through 131
407	-37 through 61	-37 through -1	1 through 61
408	-15 through 55	-15 through -1	1 through 55
409	-45 through 15	-45 through -1	1 through 15
410	-22 through 17	-22 through -1	1 through 17
411	-23 through 28	-23 through -1	1 through 28
412	-48 through 47	-48 through -1	1 through 47
413	-32 through 28	-32 through -1	1 through 28
414	-79 through 91	·79 through ·1	1 through 91
415	-82 through 108	-82 through -1	1 through 108
416	-60 through 54	-60 through -1	1 through 54
417	-108 through 53	-108 through -1	1 through 53
418	-21 through 46	-21 through -1	1 through 46
419	-32 through 300	-32 through -1	1 through 300
420	-19 through 46	-19 through -1	1 through 46
422	-30 through 27	-30 through -1	1 through 48
423	-17 through 68	-17 through -1	1 through 68
424	-17 through 68	-17 through -1	1 through 68
425	-29 through 40	-29 through -1	
426	-56 through 66	-56 through -1	1 through 40
427	-30 through 11	-30 through -1	1 through 66
428	-36 through 14	-36 through -1	1 through 11
429	-18 through 118	-18 through -1	1 through 14
430	-65 through 129	-65 through -1	1 through 118
431	-69 through 72	-69 through -1	1 through 129
432	-69 through 179	-69 through -1	1 through 72
433	-36 through 13	-36 through -1	1 through 179
434	-14 through 72	-14 through -1	1 through 13
435	-58 through 86		1 through 72
<del></del>	ugin oo	-58 through -1	1 through 86





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## CONT. TABLE V

436 437 438 439 440 441 442 443 444 445	-16 through 105 -16 through 146 -20 through 90 -15 through 56 -24 through 75 -25 through 144 -76 through 91	-16 through -1 -16 through -1 -20 through -1 -15 through -1 -24 through -1	1 through 105 1 through 146 1 through 90
438 439 440 441 442 443 444	-20 through 90 -15 through 56 -24 through 75 -25 through 144	-16 through -1 -20 through -1 -15 through -1	1 through 146 1 through 90
439 440 441 442 443 444	-15 through 56 -24 through 75 -25 through 144	-20 through -1 -15 through -1	1 through 90
440 441 442 443 444	-24 through 75 -25 through 144	-15 through -1	
441 442 443 444	-24 through 75 -25 through 144		
442 443 444	-25 through 144		1 through 56
443 444		-25 through -1	tillonfil 12
444	.70 monan 91	-76 through -1	1 through 144
	-15 through 55	-15 through -1	1 through 91
445	-33 through 348	-33 through -1	1-through 55
	-14 through 25	-14 through -1	1 through 348
446	-37 through 13	-37 through -1	1 through 25
447	-26 through 25	-26 through -1	1 through 13
448	-30 through 212		1 through 25
449	-60 through 94	-30 through -1	1 through 212
450	-61 through 28	-60 through -1	1 through 94
451	-26 through 47	-61 through -1	1 through 28
452	-34 through 20	-26 through -1	1 through 47
453	-38 through 83	-34 through -1	1 through 20
454		-38 through -1	1 through 83
455	-37 through 129	-37 through -1	1 through 129
456	-26 through 154	-26 through -1	1 through 154
457	-64 through 27	-64 through -1	1 through 27
458	-23 through 234	-23 through -1	1 through 234
459	-60 through 133	-60 through -1	1 through 133
460	-28 through 79	-28 through -1	1 through 79
461	-13 through 108	-13 through -1	1 through 108
462	-17 through 27	-17 through -1	1 through 27
463	-13 through 96	-13 through -1	1 through 96
464	-41 through 102	-41 through -1	1 through 102
465	-30 through 202	-30 through -1	1 through 202
466	-21 through 40	-21 through -1	1 through 40
467	-19 through 15	-19 through -1	1 through 15
468	-54 through 161	-54 through -1	1 through 161
	-17 through 10	-17 through -1	1 through 10
469	-24 through 61	-24 through -1	1 through 61
470	-16 through 35	-16 through -1	1 through 35
471	-43 through 24	-43 through -1	1 through 24
472	-15 through 48	-15 through -1	1 through 48
473	-58 through 121	-58 through -1	1 through 121
474	-71 through 167	-71 through -1	1 through 167
475	-37 through 141	-37 through -1	1 through 141
476	-21 through 75	-21 through -1	1 through 75
477	-24 through 17	-24 through -1	1 through 17
478	-27 through 86	-27 through -1	1 through 86
479	-18 through 232	-18 through -1	1 through 232
480	-21 through 130	-21 through -1	1 through 130
481	25 through 214	-25 through -1	1 through 214
482	-92 through 116	-92 through -1	1 through 116
483	-39 through 47	-39 through -1	1 through 47
484	-27 through 13	-27 through -1	1 through 13
485	-16 through 49	·16 through ·1	1 through 49
486	-55 through 75	-55 through -1	1 through 75
487	-84 through 125	-84 through -1	1 through 125
488	-17 through 19	-17 through -1	1 through 19
489	-29 through 15	-29 through -1	. 1 through 15



490	-52 through 111	-52 through -1	
491	-47 through 17	-47 through -1	1 through 111
492	-50 through 168	-50 through -1	1 through 17
493	-15 through 201	-15 through -1	1 through 168
494	-19 through 115	-19 through -1	1 through 201
495	-16 through 69	-16 through -1	1 through 115
496	-29 through 263		1 through 69
497	-56 through 66	-29 through -1	1 through 263
498	-28 through 31	-56 through -1	1 through 66
499	-13 through 86	-28 through -1	1 through 31
500	-13 through 86	-13 through -1	1 through 86
501	-25 through 83	-13 through -1	1 through 86
502		-25 through -1	1 through 83
503	-15 through 168	-15 through -1	1 through 168
504	-15 through 83	-15 through -1	1 through 83
505	-57 through 126	-57 through -1	1 through 126
506	-14 through 126	-14 through -1	1 through 126
507	-14 through 45	-14 through -1	1 through 45
	-36 through 65	-36 through -1	1 through 65
508	-55 through 286	-55 through -1	1 through 286
509	-42 through 66	-42 through -1	1 through 66
510	-26 through 54	-26 through -1	1 through 54
511	-44 through 114	-44 through -1	1 through 114
512	-28 through 102	-28 through -1	1 through 102
513	-62 through 137	-62 through -1	1 through 137
514	-25 through 155	-25 through -1	
		To monthi.t	1 through 155





# ·120· TABLE VI

ld	Callerati	
<u> </u>	Collection refs	Deposit Name
40		SignalTag 121-144
41	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
42		SignalTag 121-144
43	ATCC # 98920	SignalTag 67-90
44-	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
45	ATCC # 98920	SignalTag 67-90
46	ATCC # 98923	SignalTag 44-66
47	ATCC # 98920	SignalTag 67-90
48	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
49	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
50	ATCC # 98921	SignalTag 121-144
51	ATCC # 98921	SignalTag 121-144
52	ATCC # 98920	SignalTag 67-90
53	ATCC # 98923	SignalTag 44-66
54	ATCC # 98920	SignalTag 67-90
55	ATCC # 98920	SignalTag 67-90
56	ATCC # 98920	
7	ATCC # 98921	SignalTag 67-90
8	ATCC # 98920	SignalTag 121-144
9	ATCC # 98920	SignalTag 67-90
0	ATCC # 98920	SignalTag 67-90
- 		SignalTag 67-90
2	ATCC # 98923	SignalTag 44-66
3	ATCC # 98923	SignalTag 44-66
	ATCC # 98923	SignalTag 44-66
1	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
i 	ATCC # 98923	SignalTag 44-66
	ATCC # 98921	SignalTag 121-144
	ATCC # 98920	SignalTag 67-90
	ATCC # 98920	SignalTag 67-90
	ATCC # 98921	SignalTag 121-144
	ATCC # 98921	SignalTag 121-144
	ATCC # 98921	SignalTag 121-144
	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
	ATCC # 98923	SignalTag 44-66



74	14T00 # 00000	-121.
74	ATCC # 98923	SignalTag 44-66
75	ATCC # 98920	SignalTag 67-90
76	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
77	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
78	ATCC # 98921	SignalTag 121-144
79	ATCC # 98923	SignalTag 44-66
80	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
81	ATCC # 98921	SignalTag 121-144
82	ATCC # 98920	SignalTag 67-90
83	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
84	ATCC # 98923	SignalTag 44-66
85	ATCC # 98923	SignalTag 44-66
86	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
87	ATCC # 98923	SignalTag 44-66
88	ATCC # 98923	SignalTag 44-66
89	ATCC # 98923	SignalTag 44-66
90	ATCC # 98923	SignalTag 44-66
91	ATCC # 98923	SignalTag 44-66
92	ATCC # 98920	SignalTag 67-90
93	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
94	ATCC # 98923	SignalTag 44-66
95	ATCC # 98923	SignalTag 44-66
96	ATCC # 98920	SignalTag 67-90
37	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
8	ATCC # 98921	SignalTag 121-144
9	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
00	ATCC # 98921	SignalTag 121-144
01	ATCC # 98920	SignalTag 67-90
02	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
03	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
04	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
05	ATCC # 98921	SignalTag 121-144
06	ATCC # 98920	SignalTag 67-90
07	ATCC # 98920	SignalTag 67-90
08	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
09	ATCC # 98923	SignalTag 44-66
10	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120





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#### 111 ATCC # 98922 SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120. 112 ATCC # 98920 SignalTag 67-90 113 ATCC # 98920 SignalTag 67-90 114 ATCC # 98923 SignalTag 44-66 115 ATCC # 98922 SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120 116 ATCC # 98920 SignalTag 67-90 117 ATCC # 98922 SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120 118 ATCC # 98922 SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120 119 ATCC # 98922 SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120 120 ATCC # 98922 SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120 121 ATCC # 98923 SignalTag 44-66 122 ATCC # 98920 SignalTap 67-90 123 ATCC # 98920 SignalTag 67-90 124 ATCC # 98922 SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120 125 ECACC # 98121506 SignalTag 11121998 126 ECACC # 98121506 SignalTag 11121998 127 ECACC # 98121506 SignalTag 11121998 128 ECACC # 98121506 SignalTag 11121998 129 ECACC # 98121506 Signal Tag 11121998 130 ECACC # 98121506 Signal Tag 11121998 131 ECACC # 98121506 Signal Tag 11121998 132 ECACC # 98121506 SignalTag 11121998 133 ECACC # 98121506 SignalTag 11121998 134 ECACC # 98121506 SignalTag 11121998 135 ECACC # 98121506 SignalTag 11121998 136 ECACC # 98121506 SignalTag 11121998 137 ECACC # 98121506 Signal Tag 11121998 138 ECACC # 98121506 Signal Tag 11121998 139 ECACC # 98121506 SignalTag 11121998 140 ECACC # 98121506 Signal Tag 11121998



## **TABLE VII**

Internal designation number	SEQ ID NO	Type of sequence
20-5-2-C3-CL0_4	40	DNA
20-8-4-A11-CL2_6	41	DNA
21-1-4-F2-CL11_1	42	DNA
22-11-2-H9-CL1_1	43	DNA
25-7-3-D4-CLO_2	44	DNA
26-27-3-D7-CL0_1	45	DNA
26-35-4-H9-CL1_1	46	DNA
26-45-2-C4-CL2_6	47	DNA
27-1-2-B3-CLO_1	48	DNA
27-1-2-B3-CLO_2	49	DNA
27-19-3-G7-CL11_2	50	DNA
33-10-4-E2-CL13_4	51	DNA
33-10-4-H2-CL2_2	52	DNA
33-110-4-A5-CL1_1	53	DNA
33-13-1-C1-CL1_1	54	DNA
33-30-2-A6-CL0_1	55	DNA
33-35-4-F4-CL1_2	56	DNA
33-35-4-G1-CL1_2	57	DNA
33-36-3-E2-CL1_1	58	DNA
33-36-3-E2-CL1_2	59	DNA
33-36-3-F2-CL2_2	60	DNA
33-4-2-G5-CL2_1	61	DNA
33-49-1-H4-CL1_1	62	DNA
33-66-2-B10-CL4_1	63	DNA
33-97-4-G8-CL2_2	64	DNA
33-98-4-C1-CL1_3	65	DNA
47-14-1-C3-CLO_5	66	DNA
47-15-1-E11-CLO_1	67	DNA
47-15-1-H8-CLO_2	68	DNA
48-1-1-H7-CLO_1	69	DNA
48-1-1-H7-CLO_4	70	DNA
48-1-1-H7-CLO_5	71	DNA
48-3-1-H9-CLO_6	72	DNA
48-54-1-G9-CL2_1	73	DNA





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	48-54-1-G9-CL3_1	74	DNA
	48-7-4-H2-CL2_2	75	DNA
	51-11-3-D5-CL1_3	76	DNA
	51-11-3-G9-CLO_1	77	DNA
	51-15-4-A12-CL11_3	78	DNA
	51-17-4-A4-CL3_1	79	DNA
	51-2-3-F10-CL1_5	80	DNA
	51-2-4-F5-CL11_2	81	DNA
	51-27-4-F2-CLO_2	82	DNA
	51-34-3-F8-CLO_2	83	DNA
	57-1-4-E2-CL1_2	84	DNA
	57-19-2-G8-CL2_1	85	DNA
	57-27-3-G10-CL2_2	86	DNA
	58-33-3-B4-CL1_2	- 87	DNA
	58-34-3-C9-CL1_2	88	DNA
	58-4-4-G2-CL2_1	89	DNA
	58-48-1-G3-CL2_4	90	DNA .
	58-6-1-H4-CL1_1	91	DNA
I	60-12-1-E11-CL1_2	92	DNA
I	65-4-4-H3-CL1_1	93	DNA
	74-5-1-E4-CL1_2	94	DNA
	76-13-3-A9-CL1_2	95	DNA
	76-16-1-D6-CL1_1	96	DNA
	76-28-3-A12-CL1_5	97	DNA
	76-42-2-F3-CLO_1	98	DNA
	77-16-4-G3-CL1_3	99	DNA
	77-39-4-H4-CL11_4	100	DNA
	78-24-3-H4-CL2_1	101	DNA
	78-27-3-D1-CL1_6	102	DNA
	78-28-3-D2-CLO_2	103	DNA
	78-7-1-G5-CL2_6	104	DNA
-	84-3-1-G10-CL11_6	105	DNA
	58-48-4-E2-CLO_1	106	DNA
	23-12-2-G6-CL1_2	107	DNA
_	25-8-4-B12-CLO_5	108	DNA
	26-44-3-C5-CL2_1	109	DNA
_	27-1-2-B3-CLO_3	110	DNA
_			l



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		.20
30-12-3-G5-CLO_1	111	DNA
33-106-2-F10-CL1_3	112	DNA
33-28-4-D1-CLO_1	113	DNA
33-31-3-C8-CL2_1	114	DNA
48-24-1-D2-CL3_2	115	DNA
48-46-4-A11-CL1_4	116	DNA
51-1-4-C1-CL0_2	117	DNA
51-39-3-H2-CL1_2	118	DNA
51-42-3-F9-CL1_1	119	DNA
51-5-3-G2-CL0_4	120	DNA
57-18-4-H5-CL2_1	121	DNA
76-23-3-G8-CL1_1	122	DNA
76-23-3-G8-CL1_3	123	DNA
78-8-3-E6-CLO_1	124	DNA
19-10-1-C2-CL1_3	125	DNA
33-11-1-B11-CL1_2	126	DNA
33-113-2-B8-CL1_2	127	DNA
33-19-1-C11-CL1_1	128	DNA
33-61-2-F6-CL0_2	129	DNA
47-4-4-C6-CL2_2	130	DNA
48-54-1-G9-CL1_1	131	DNA
51-43-3-G3-CL0_1	132	DNA
55-1-3-D11-CLO_1	133	DNA
58-14-2-D3-CL1_2	134	DNA
58-35-2-B6-CL2_3	135	DNA
76-18-1-F6-CL1_1	136	DNA
76-23-3-G8-CL2_2	137	DNA
76-30-3-B7-CL1_1	138	DNA
78-21-3-G7-CL2_1	139	DNA
58-45-4-B11-CL13_2	140	DNA
20-5-2-C3-CL0_4	141	PRT
20-8-4-A11-CL2_6	142	PRT
21-1-4-F2-CL11_1	143	PRT
22-11-2-H9-CL1_1	144	PRT
25-7-3-D4-CL0_2	145	PRT
26-27-3-D7-CLO_1	146	PRT
26-35-4-H9-CL1_1	147	PRT





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			-120-	
	26-45-2-C4-CL2_6	148	PRT	
	27-1-2-B3-CLO_1	149	PRT	
	27-1-2-B3-CL0_2	150	PRT	
	27-19-3-G7-CL11_2	151	PRT	
	33-10-4-E2-CL13_4	152	PRT	
	33-10-4-H2-CL2_2	153	PRT	
	33-110-4-A5-CL1_1	154	PRT	
	33-13-1-C1-CL1_1	155	PRT	
	33-30-2-A6-CLO_1	156	PRT	
	33-35-4-F4-CL1_2	157	PRT	
	33-35-4-G1-CL1_2	158	PRT	
L	33-36-3-E2-CL1_1	159	PRT	
	33-36-3-E2-CL1_2	160	PRT	
	33-36-3-F2-CL2_2	161	PRT	
L	33-4-2-G5-CL2_1	162	PRT	—
L	33-49-1-H4-CL1_1	163	PRT	
L	33-66-2-B10-CL4_1	164	PRT	
L	33-97-4-G8-CL2_2	165	PRT	-
L	33-98-4-C1-CL1_3	166	PRT	$\dashv$
L	47-14-1-C3-CL0_5	167	PRT	$\dashv$
	47-15-1-E11-CLO_1	168	PRT	$\dashv$
	47-15-1-H8-CLO_2	169	PRT	$\dashv$
	48-1-1-H7-CLO_1	170	PRT	$\dashv$
	48-1-1-H7-CLO_4	171	PRT	$\dashv$
	48-1-1-H7-CLO_5	172	PRT	$\dashv$
	48-3-1-H9-CLO_6	173	PRT	$\dashv$
	48-54-1-G9-CL2_1	174	PRT	+
	48-54-1-G9-CL3_1	175	PRT	$\dagger$
	48-7-4-H2-CL2_2	176	PRT	1
	51-11-3-D5-CL1_3	177	PRT	1
	51-11-3-G9-CLO_1	178	PRT	1
	51-15-4-A12-CL11_3	179	PRT	1
	51-17-4-A4-CL3_1	180	PRT	1
	51-2-3-F10-CL1_5	181	PRT	
	51-2-4-F5-CL11_2	182	PRT	
	51-27-4-F2-CLO_2	183	PRT	
	51-34-3-F8-CLO_2	184	PRT	
		·		





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57-1-4-E2-CL1_2	185	PRT
57-19-2-G8-CL2_1	186	PRT
57-27-3-G10-CL2_2	187	PRT
58-33-3-B4-CL1_2	188	PRT
58-34-3-C9-CL1_2	189	PRT
58-4-4-G2-CL2_1	190	PRT
58-48-1-G3-CL2_4	191	PRT
58-6-1-H4-CL1_1	192	PRT
60-12-1-E11-CL1_2	193	PRT
65-4-4-H3-CL1_1	194	PRT
74-5-1-E4-CL1_2	195	PRT
76-13-3-A9-CL1_2	196	PRT
76-16-1-D6-CL1_1	197	PRT
76-28-3-A12-CL1_5	198	PRT
76-42-2-F3-CLO_1	199	PRT
77-16-4-G3-CL1_3	200	PRT
77-39-4-H4-CL11_4	201	PRT
78-24-3-H4-CL2_1	202	PRT
78-27-3-D1-CL1_6	203	PRT
78-28-3-D2-CLO_2	204	PRT
78-7-1-G5-CL2_6	205	PRT
84-3-1-G10-CL11_6	206	PRT
58-48-4-E2-CLO_1	207	PRT
23-12-2-G6-CL1_2	208	PRT
25-8-4-B12-CL0_5	209	PRT
26-44-3-C5-CL2_1	210	PRT
27-1-2-B3-CL0_3	211	PRT
30-12-3-G5-CL0_1	212	PRT
33-106-2-F10-CL1_3	213	PRT
33-28-4-D1-CLO_1	214	PRT
33-31-3-C8-CL2_1	215	PRT
48-24-1-D2-CL3_2	216	PRT
48-46-4-A11-CL1_4	217	PRT
51-1-4-C1-CL0_2	218	PRT
51-39-3-H2-CL1_2	219	PRT
51-42-3-F9-CL1_1	220	PRT
51-5-3-G2-CL0_4	221	PRT
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	57-18-4-H5-CL2_1	222	PRT	_
	76-23-3-G8-CL1_1	223	PRT	-
	76-23-3-G8-CL1_3	224	PRT	-
	78-8-3-E6-CLO_1	225	PRT	-
	19-10-1-C2-CL1_3	226	PRT	-
	33-11-1-B11-CL1_2	227	PRT	-
	33-113-2-B8-CL1_2	228	PRT	=
	33-19-1-C11-CL1_1	229	PRT	-
	33-61-2-F6-CLO_2	230	PRT	-
	47-4-4-C6-CL2_2	231	PRT	-
	48-54-1-G9-CL1_1	232	PRT	-
	51-43-3-G3-CLO_1	233	PRT	-
	55-1-3-D11-CLO_1	234	PRT	-
ı	58-14-2-D3-CL1_2	235	PRT	-
ı	58-35-2-B6-CL2_3	236	PRT	
	76-18-1-F6-CL1_1	237	PRT	1
	76-23-3-G8-CL2_2	238	PRT	I
L	76-30-3-B7-CL1_1	239	PRT	ı
L	78-21-3-G7-CL2_1	240	PRT	
L	58-45-4-B11-CL13_2	241	PRT	
L	20-6-1-D11-FL2	242	DNA	
	20-8-4-A11-FL2	243	DNA	
_	22-6-2-C1-FL2	244	DNA	
	22-11-2-H9-FL1	245	DNA	
	23-8-3-B1-FL1	246	DNA	
_	24-3-3-C6-FL1	247	DNA	
_	24-4-1-H3-FL1	248	DNA	
_	26-45-2-C4-FL2	249	DNA	
_	26-48-1-H10-FL1	250	DNA	
	26-49-1-A5-FL2	251	DNA	
_	30-6-4-E3-FL3	252	DNA	
	33-6-1-G11-FL1	253	DNA	
	33-8-1-A3-FL2	254	DNA	
_	33-11-3-C6-FL1	255	DNA	
_	33-14-4-E1-FL1	256	DNA	
_	33-21-2-D5-FL1	257	DNA	
_	33-26-4-E10-FL1	258	DNA	



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		120
33-27-1-E11-FL1	259	DNA
33-28-4-D1-FL1	260	DNA
33-28-4-E2-FL2	261	DNA
33-30-4-C4-FL1	262	DNA
33-35-4-F4-FL1	263	DNA
33-36-3-F2-FL2	264	DNA
33-52-4-F9-FL2	265	DNA
33-52-4-H3-FL1	266	DNA
33-59-1-87-FL1	267	DNA
33-71-1-A8-FL1	268	DNA
33-72-2-B2-FL1	269	DNA
33-105-2-C3-FL1	270	DNA
33-107-4-C3-FL1	271	DNA
33-110-2-64-FL1	272	DNA
47-7-4-D2-FL2	273	DNA
47-10-2-G12-FL1	274	DNA
47-14-3-D8-FL1	275	DNA
47-18-3-C2-FL1	276	DNA
47-18-3-G5-FL2	277	DNA
47-18-4-E3-FL2	278	DNA
48-3-1-H9-FL3	279	DNA
48-4-2-H3-FL1	280	DNA
48-6-1-C9-FL1	281	DNA
48-7-4-H2-FL2	282	DNA
48-8-1-D8-FL3	283	DNA
48-13-3-H8-FL1	284	DNA
48-19-3-A7-FL1	285	DNA
48-19-3-G1-FL1	286	DNA
48-25-4-D8-FL1	287	DNA
48-21-4-H4-FL1	288	DNA
48-26-3-B8-FL2	289	DNA
48-29-1-E2-FL1	290	DNA
48-31-3-F7-FL1	291	DNA
48-47-3-A5-FL1	292	DNA
51-1-1-G12-FL1	293	DNA
51-1-4-E9-FL3	294	DNA
	1	<u> </u>

295

DNA

51-1-4-E9-FL2





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			-130-		
	51-2-1-E10-FL1		296	DNA	
	51-2-3-F10-FL1		297	DNA	_
	51-2-4-F5-FL1		298	DNA	
	51-3-3-B10-FL2		299	DNA	
	51-3-3-B10-FL3	3	00	DNA	
	51-7-3-G3-FL1	3	01	DNA	
	51-10-3-D11-FL1	3	02	DNA	
	51-11-3-D5-FL1	3	03	DNA	
	51-13-1-F7-FL3	31	04	DNA	
	51-15-4-H10-FL1	30	)5	DNA	
	51-17-4-A4-FL1	30	16	DNA	-
	51-18-1-C3-FL1	30	7	DNA	
	51-25-3-F3-FL1	30	8	DNA	
ĺ	51-27-1-E8-FL1	30	9	DNA	
	51-28-2-G1-FL2	310	)	DNA	
	51-39-3-H2-FL1	31		DNA	
	51-42-3-F9-FL1	312	-	DNA	_
	51-44-4-H4-FL1	313		DNA	
L	55-1-3-H10-FL1	314		DNA	$\dashv$
L	55-5-4-A6-FL1	315	<del>-  </del> -	DNA	$\dashv$
L	58-26-3-D1-FL1	316		DNA	$\dashv$
L	57-18-1-D5-FL1	317		DNA	$\dashv$
	57-27-3-A11-FL1	318		DNA	$\dashv$
_	57-27-3-G10-FL2	319		DNA	$\dashv$
	58-10-3-D12-FL1	320		DNA	$\dashv$
	58-11-1-G10-FL1	321		DNA	$\dashv$
	58-11-2-G8-FL2	322		DNA	$\dashv$
	58-36-3-A9-FL2	323		DNA	$\dashv$
_	58-38-1-A2-FL2	324		DNA	$\dashv$
	58-38-1-E5-FL1	325		DNA	$\dashv$
	58-44-2-B3-FL3	326		DNA	┨
_	58-45-3-H11-FL1	327		DNA	
	58-53-2-B12-FL2	328		DNA	$\mathbf{I}$
_	59-9-4-A10-FL1	329	+	DNA	1
_	60-16-3-A6-FL1	330		DNA	1
	60-17-3-G8-FL2	331	_	DNA	
	62-5-4-B10-FL1	332		DNA	





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		131.
65-4-4-H3-FL1	333	DNA
74-3-1-B9-FL1	334	DNA
76-4-1-G5-FL1	335	DNA
76-7-3-A12-FL1	336	DNA
76-16-4-C9-FL3	337	DNA
76-30-3-B7-FL1	338	DNA
77-5-1-C2-FL1	339	DNA
77-5-4-E7-FL1	340	DNA
77-11-1-A3-FL1	341	DNA
77-16-3-D7-FL1	342	DNA
77-16-4-G3-FL1	343	DNA
77-25-1-A6-FL1	344	DNA
77-26-2-F2-FL3	345	DNA
78-6-2-E3-FL2	346	DNA
78-7-1-G5-FL2	347	DNA
78-16-2-C2-FL1	348	DNA
78-18-3-B4-FL3	349	DNA
78-20-1-G11-FL1	350	DNA
78-22-3-E10-FL1	351	DNA
78-24-2-B8-FL1	352	DNA
78-24-3-A8-FL1	353	DNA
78-24-3-H4-FL2	354	DNA
78-25-1-F11-FL1	355	DNA
78-26-1-B5-FL1	356	DNA
78-27-3-D1-FL1	357	DNA
78-29-1-B2-FL1	358	DNA
78-29-4-B6-FL1	359	DNA
14-1-3-E6-FL1	360	DNA
30-9-1-G8-FL2	361	DNA
33-10-4-H2-FL2	362	DNA
33-10-4-H2-FL1	363	DNA
74-10-3-C9-FL2	364	DNA
33-97-4-G8-FL3	365	DNA
33-97-4-G8-FL2	366	DNA
33-104-4-H4-FL1	367	DNA
47-2-3-B3-FL1	368	DNA
47-37-4-G11-FL1	369	DNA
	<u></u>	





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	57.05 4.50		-132.
	57-25-1-F10-FL2	370	DNA
	58-19-3-D3-FL1	371	DNA
	58-34-3-C9-FL2	372	DNA
	58-48-4-E2-FL2	373	DNA
	76-21-1-C4-FL1	374	DNA
	78-26-2-H7-FL1	375	DNA
	77-20-2-E11-FL1	376	DNA
	47-1-3-F7-FL2	377	DNA
	20-6-1-D11-FL2	378	PRT
	20-8-4-A11-FL2	379	PRT
	22-6-2-C1-FL2	380	PRT
	22-11-2-H9-FL1	381	PRT
i	23-8-3-B1-FL1	382	PRT
į	24-3-3-C6-FL1	383	PRT
	24-4-1-H3-FL1	384	PRT
	26-45-2-C4-FL2	385	PRT
	26-48-1-H10-FL1	386	PRT
	26-49-1-A5-FL2	387	PRT
L	30-6-4-E3-FL3	388	PRT
L	33-6-1-G11-FL1	389	PRT
L	33-8-1-A3-FL2	390	PRT
L	33-11-3-C6-FL1	391	PRT
	33-14-4-E1-FL1	392	PRT
_	33-21-2-D5-FL1	393	PRT
	33-26-4-E10-FL1	394	PRT
_	33-27-1-E11-FL1	395	PRT
	33-28-4-D1-FL1	396	PRT
_	33-28-4-E2-FL2	397	PRT
	33-30-4-C4-FL1	398	PRT
	33-35-4-F4-FL1	399	PRT
	33-36-3-F2-FL2	400	PRT
_	33-52-4-F9-FL2	401	PRT
	33-52-4-H3-FL1	402	PRT
_	33-59-1-B7-FL1	403	PRT
	33-71-1-A8-FL1	404	PRT
_	33-72-2-B2-FL1	405	PRT
_	33-105-2-C3-FL1	406	PRT



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		. 133.
33-107-4-C3-FL1	407	PRT
33-110-2-G4-FL1	408	PRT
47-7-4-D2-FL2	409	PRT
47-10-2-G12-FL1	410	PRT
47-14-3-D8-FL1	411	PRT
47-18-3-C2-FL1	412	PRT
47-18-3-G5-FL2	413	PRT
47-18-4-E3-FL2	414	PRT
48-3-1-H9-FL3	415	PRT
48-4-2-H3-FL1	416	PRT
48-6-1-C9-FL1	417	PRT
48-7-4-H2-FL2	418	PRT
48-8-1-D8-FL3	419	PRT
48-13-3-H8-FL1	420	PRT
48-19-3-A7-FL1	421	PRT
48-19-3-G1-FL1	422	PRT
48-25-4-D8-FL1	423	PRT
48-21-4-H4-FL1	424	PRT
48-26-3-B8-FL2	425	PRT
48-29-1-E2-FL1	426	PRT
48-31-3-F7-FL1	427	PRT
48-47-3-A5-FL1	428	PRT
51-1-1-G12-FL1	429	PRT
51-1-4-E9-FL3	430	PRT
51-1-4-E9-FL2	431	PRT
51-2-1-E10-FL1	432	PRT
51-2-3-F10-FL1	433	PRT
51-2-4-F5-FL1	434	PRT
51-3-3-B10-FL2	435	PRT
51-3-3-B10-FL3	436	PRT
51-7-3-G3-FL1	437	PRT
51-10-3-D11-FL1	438	PRT
51-11-3-D5-FL1	439	PRT
51-13-1-F7-FL3	440	PRT
51-15-4-H10-FL1	441	PRT
51-17-4-A4-FL1	442	PRT
51-18-1-C3-FL1	443	PRT
**************************************	L	





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		104				
	51-25-3-F1	444	PRT			
	51-27-1-E8-FL1	445	PRT			
	51-28-2-G1-FL2	446	PRT			
	51-39-3-H2-FL1	447	PRT			
	51-42-3-F9-FL1	448	PRT			
	51-44-4-H4-FL1	449	PRT			
	55-1-3-H10-FL1	450	PRT			
	55-5-4-A6-FL1	451	PRT			
	58-26-3-D1-FL1	452	PRT			
	57-18-1-D5-FL1	453	PRT			
	57-27-3-A11-FL1	454	PRT			
	57-27-3-G10-FL2	455	PRT			
	58-10-3-D12-FL1	456	PRT			
	58-11-1-G10-FL1	457	PRT			
	58-11-2-G8-FL2	458	PRT			
	58-36-3-A9-FL2	459	PRT			
	58-38-1-A2-FL2	460	PRT			
58-38-1-E5-FL1		461	PRT			
L	58-44-2-B3-FL3	462	PRT			
L	58-45-3-H11-FL1	463	PRT			
58-53-2-B12-FL2		464	PRT			
L	59-9-4-A 10-FL1	465	PRT			
L	60-16-3-A6-FL1	466	PRT			
	60-17-3-G8-FL2	467	PRT			
	62-5-4-B10-FL1	468	PRT			
	65-4-4-H3-FL1	469	PRT			
	74-3-1-B9-FL1	470	PRT			
	76-4-1-G5-FL1	471	PRT			
	76-7-3-A12-FL1	472	PRT			
	76-16-4-C9-FL3	473	PRT			
	76-30-3-B7-FL1	474	PRT			
_	77-5-1-C2-FL1	475	PRT			
	77-5-4-E7-FL1	476	PRT			
	77-11-1-A3-FL1	477	PRT			
	77-16-3-D7-FL1	478	PRT			
	77-16-4-G3-FL1	479	PRT			
	77-25-1-A6-FL1	480	PRT			
		<del></del>				





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77-26-2-F2-FL3	481	PRT
78-6-2-E3-FL2	482	PRT
78-7-1-G5-FL2	483	PRT
78-16-2-C2-FL1	484	PRT
78-18-3-B4-FL3	485	PRT
78-20-1-G11-FL1	486	PRT
78-22-3-E10-FL1	487	PRT-
78-24-2-B8-FL1	488	PRT
78-24-3-A8-FL1	489	PRT
78-24-3-H4-FL2	490	PRT
78-25-1-F11-FL1	491	PRT
78-26-1-B5-FL1	492	PRT
78-27-3-D1-FL1	493	PRT
78-29-1-B2-FL1	494	PRT
78-29-4-B6-FL1	495	PRT
14-1-3-E6-FL1	496	PRT
30-9-1-G8-FL2	497	PRT
33-10-4-H2-FL2	498	PRT
33-10-4-H2-FL1	499	PRT
74-10-3-C9-FL2	500	PRT
33-97-4-G8-FL3	501	PRT
33-97-4-G8-FL2	502	PRT
33-104-4-H4-FL1	503	PRT
47-2-3-B3-FL1	504	PRT
47-37-4-G11-FL1	505	PRT
57-25-1-F10-FL2	506	PRT
58-19-3-D3-FL1	507	PRT
58-34-3-C9-FL2	508	PRT
58-48-4-E2-FL2	509	
76-21-1-C4-FL1	510	PRT
78-26-2-H7-FL1	510	PRT
77-20-2-E11-FL1		PRT
47-1-3-F7-FL2	512	PRT
47-1-04 7/FL2	513	PRT







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## **TABLE VIII**

ID	Locations	PROSITE Signature Name
195	110-121	Aldehyde dehydrogenases csyteine active site
221	28-37	ATP synthase alpha and beta subunits signature
223	171-181	Regulator of chromosome condensation (RCC1) signature 2
225	90-112	Phosphatidylethanolamine-binding protein family signature
226	10-34	Protein kinases ATP-binding region signature





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#### WHAT IS CLAIMED IS:

A purified or isolated nucleic acid comprising the sequence of one of SEQ ID NOs: 40-140 and 242 377 or a sequence complementary thereto.

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- 2. A purified or isolated nucleic acid comprising at least 10 consecutive bases of the sequence of one of 5 SEO ID NOs: 40-140 and 242-377 or one of the sequences complementary thereto.
  - 3. A purified or isolated nucleic acid comprising the full coding sequences of one of SEQ ID NOs: 40, 42-44, 46, 48, 49, 51, 53, 60, 62-72, 76-78, 80-83, 85-88, 90, 93, 94, 97, 99-102, 104, 107-125, 127, 132, 135-138, 140 and 242-377 wherein the full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein.
- 4. A purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein.
- 5. A purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40, 42-46, 48, 49, 51, 53, 57, 60, 62-73, 76-78, 80-83, 85-88, 90, 93-95, 97, 99-102, 104, 107-125, 127, 128, 130, 132, 134-140 and 242-377 which encode the signal peptide.
  - 6. A purified or isolated nucleic acid encoding a polypeptide having the sequence of one of the sequences of SEQ ID NOs: 141-241 and 378-513.
- 7. A purified or isolated nucleic acid encoding a polypeptide having the sequence of a mature protein included in one of the sequences of SEO ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-20 189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.
  - 8. A purified or isolated nucleic acid encoding a polypeptide having the sequence of a signal peptide included in one of the sequences of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.
    - A purified or isolated protein comprising the sequence of one of SEQ ID NOs: 141-241 and 378-513.
- 25 10. A purified or isolated polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513.
  - 11. An isolated or purified polypeptide comprising a signal peptide of one of the polypeptides of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.
- 30 12. An isolated or purified polypeptide comprising a mature protein of one of the polypeptides of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.
  - 13. A method of making a protein comprising one of the sequences of SEQ ID NO: 141-241 and 378-513, comprising the steps of:

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cDNA.





obtaining a cDNA comprising one of the sequences of sequence of SEQ ID NO: 40-140 and 242-377; inserting said cDNA in an expression vector such that said cDNA is operably linked to a promoter; and introducing said expression vector into a host cell whereby said host cell produces the protein encoded by said

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- 5 14. The method of Claim 13, further comprising the step of isolating said protein.
  - 15. A protein obtainable by the method of Claim 14.
  - A host cell containing a recombinant nucleic acid of Claim 1.
  - 17. A purified or isolated antibody capable of specifically binding to a protein having the sequence of one of SEQ ID NOs: 141-241 and 378-513.
- 10 18. In an array of polynucleotides of at least 15 nucleotides in length, the improvement comprising inclusion in said array of at least one of the sequences of SEQ ID NOs: 40-140 and 242-377, or one of the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or a fragment thereof of at least 15 consecutive nucleotides.
- A purified or isolated nucleic acid of at least 15 bases capable of hybridizing under stringent
   conditions to the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary to one of the sequences of SEQ ID NOs: 40-140 and 242-377.
  - 20. A purified or isolated antibody capable of binding to a polypeptide comprising at least 10 consecutive amino acids of the sequence of one of SEQ ID NOs: 141-241 and 378-513.

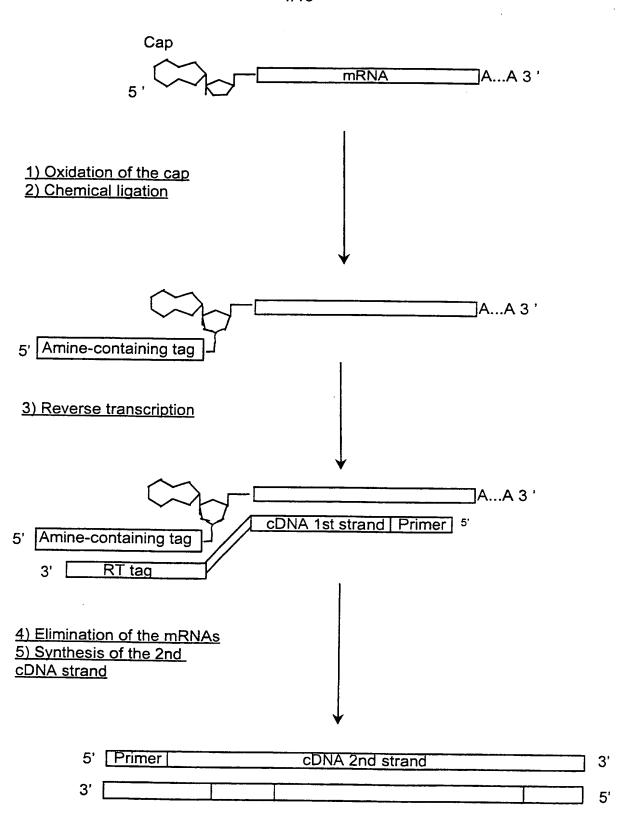


Figure 1



Minimum signal peptide score	false positive rate	false negative rate	proba(0.1)	proba(0.2)
3,5	0,121	0,036	0,467	0,664
4	0,096	0,06	0,519	0,708
4,5	0,078	0,079	0,565	0,745
5	0,062	0,098	0,615	0,782
5,5	0,05	0,127	0,659	0,813
6	0,04	0,163	0,694	0,836
6,5	0,033	0,202	0,725	0,855
7	0,025	0,248	0,763	0,878
7,5	0,021	0,304	0,78	0,889
8	0,015	0,368	0,816	0,909
8,5	0,012	0,418	0,836	0,92
9	0,009	0,512	0,856	0,93
9,5	0,007	0,581	0,863	0,934
10	0,006	0,679	0,835	0,919

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# influence of minimum score on signal peptide recognition

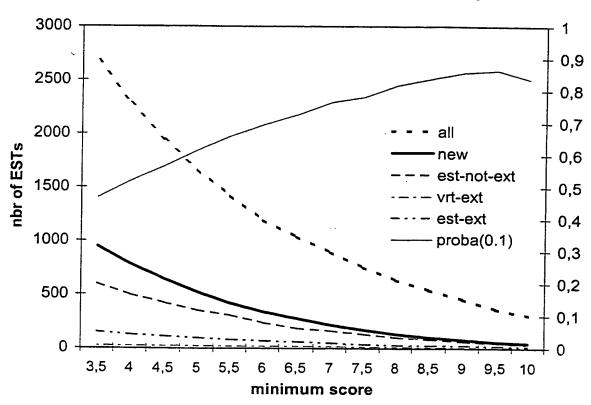


FIGURE 3



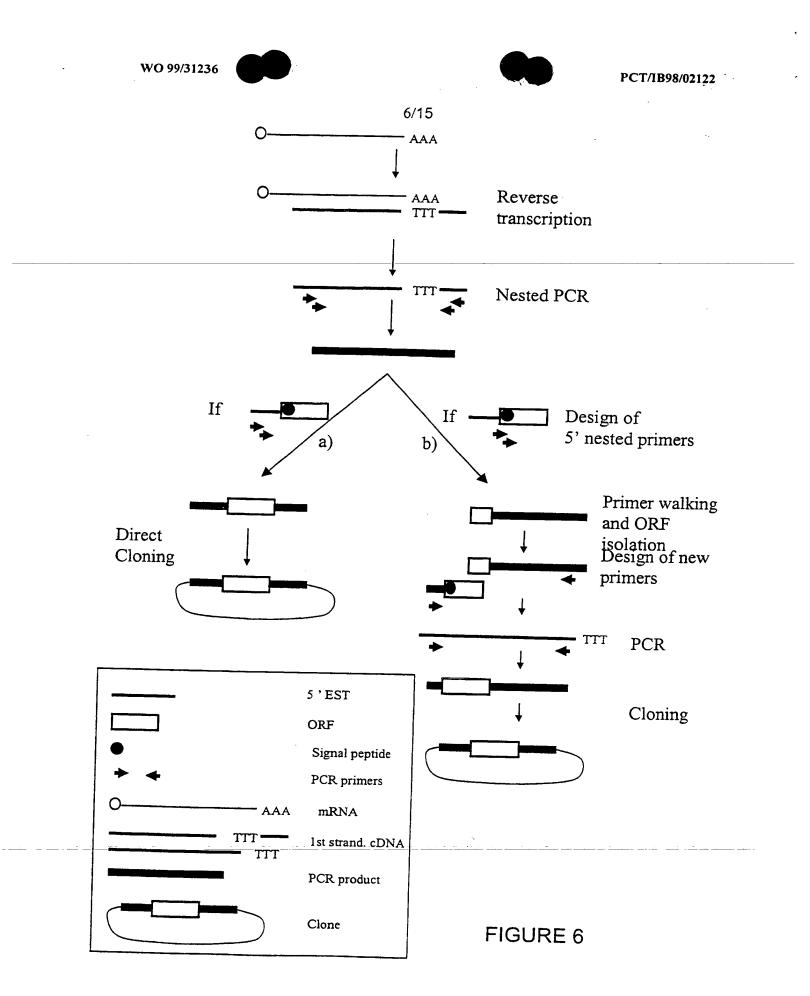
		<del></del>	T		
Minimum signal peptide score		New ESTs	ESTs matching public EST closer than 40 bp from beginning	ESTs extending known mRNA more than 40 bp	ESTs extending public EST more than 40 bp
3,5	2674	947	599	23	150
4	2278	784	499	23	126
4,5	1943	647	425	22	112
5	1657	523	353	21	96
5,5	1417	419	307	19	80
6	1190	340	238	18	68
6,5	1035	280	186	18	60
7	893	219	161	15	48
7,5	753	173	132	12	36
8	636	133	101	11	29
8,5	543	104	83	8	26
9	456	81	63	6	24
9,5	364	57	48	6	18
10	303	47	35	6	15

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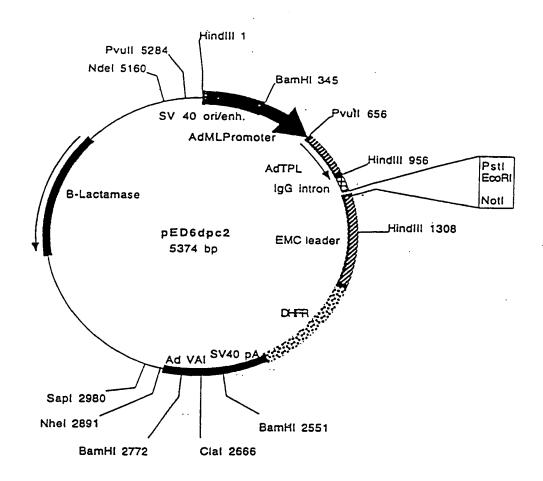
FIGURE 4



	7				
Tissue	All ESTs	New ESTs	ESTs matching public EST closer than 40 bp from beginning	ESTs extending known mRNA more than 40 bp	ESTs extending public EST more than 40 bp
Brain	329	131	75	3	24
Cancerous prostate	134	40	37	1	6
Cerebellum	17	9	1	ó	6
Colon	21	11	4	Ö	öl
Dystrophic muscle	41	18	8	0	1
Fetal brain	70	37	16	0	1
Fetal kidney	227	116	46	1	19
Fetal liver	13	7	2	ó	0
Heart	30	15	7	ő	1
Hypertrophic prostate	86	23	22	2	2
Kidney	10	7	3	0	0
Large intestine	21	8	4	Ö	1
Liver	23	9	6	0	o
Lung	24	12	4	ő	1
Lung (cells)	57	38	6	Õ	4
Lymph ganglia	163	60	23	2	12
Lymphocytes	23	6	4	ō	2
Muscle	33	16	6	Ö	4
Normal prostate	181	61	45	7	11
Ovary	90	57	12	1	2
Pancreas	48	11	6	0	1
Placenta	24	5	1	0	
Prostate	34	16	4	Ö	0 2 1
Spleen	56	28	10	Ō	1
Substantia nigra	108	47	27	1	6
Surrenals	15	3	3	1	ő
Testis	131	68	25	1	
Thyroid	17	8	2	ó	8 2 3
Umbilical cord	55	17	12	1	3
Uterus	28	15	3	ò	2
Non tissue-specific	568	48	177	2	28
Total	2677	947	601	23	150



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Plasmid name: pED6dpc2 Plasmid size: 5374 bp



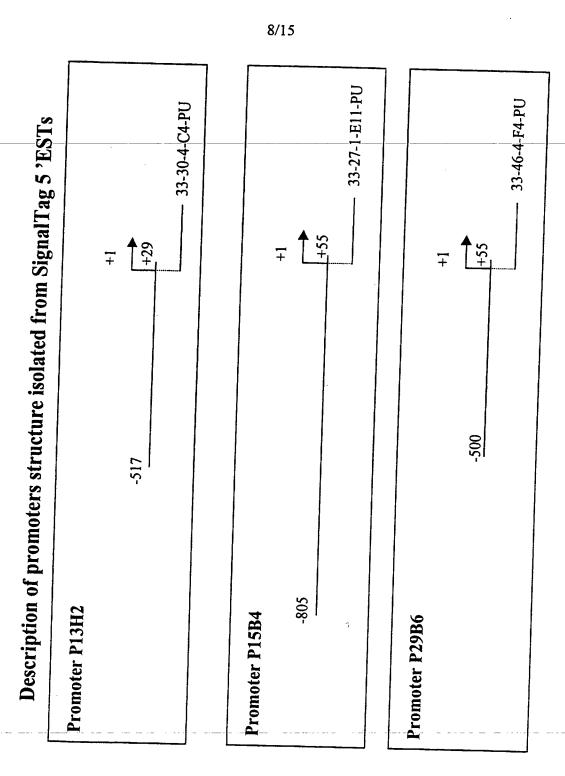


FIGURE 8



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# Description of Transcription Factor Binding Sites present on promoters isolated from SignalTag sequences

## Promoter sequence P13H2 (546 bp):

Matrix	Position	Orientation	Score	Length	Sequence
CMYB_01	-502	+	0.983	9	TGTCAGTTG
MYOD_Q6	-501	<b>-</b> .	0.961	10	CCCAACTGAC
S8_01	-444	-	0.960	11	AATAGAATTAG
S8_01	<del>-4</del> 25	+	0.966	11	AACTAAATTAG
DELTAEF1_01	-390	•	0.960	11	GCACACCTCAG
GATA_C	-364	•	0.964	11	AGATAAATCCA
CMYB_01	-349	+	0.958	9	CTTCAGTTG
GATA1_02	-343	+	0.959	14	TTGTAGATAGGACA
GATA_C	-339	+	0.953	11	AGATAGGACAT
TAL1ALPHAE47_01	-235	+	0.973	16	CATAACAGATGGTAAG
TAL1BETAE47_01	-235	+	0.983	16	CATAACAGATGGTAAG
TAL1BETAITF2_01	-235	+	0.978	16	CATAACAGATGGTAAG
MYOD_Q6	-232	•	0.954	10	ACCATCTGTT
GATA1_04	-217	•	0.953	13	TCAAGATAAAGTA
IK1_01	-126	+	0.963	13	AGTTGGGAATTCC
IK2_01	-126	+	0.985	12	AGTTGGGAATTC
CREL_01	-123	+	0.962	10	TGGGAATTCC
GATA1_02	-96	+	0.950	14	TCAGTGATATGGCA
SRY_02	-41	-	0.951	12	TAAAACAAAACA
E2F_02	<b>-3</b> 3	+	0.957	8	TTTAGCGC
MZF1_01	-5	-	0.975	8	TGAGGGGA

## Promoter sequence P15B4 (861bp):

Matrix	Position	Orientation	Score	Length	Sequence
NFY_Q6	-748	-	0.956	11	GGACCAATCAT
MZF1_01	-738	+	0.962	8	CCTGGGGA
CMYB_01	-684	+	0.994	9	TGACCGTTG
VMYB_02	-682	•	0.985	9	TCCAACGGT
STAT_01	-673	+	0.968	9	TTCCTGGAA
STAT_01	-673	•	0.951	9	TTCCAGGAA
MZF1_01	-556	-	0.956	8	TTGGGGGA
IK2_01	-451	+	0.965	12	GAATGGGATTTC
MZF1_01	-424	+	0.986	8	AGAGGGGA
SRY_02	-398	-	0.955	12	GAAAACAAAACA
MZF1_01	-216	+	0.960	8	GAAGGGGA
MYOD_Q6	-190	+	0.981	10	AGCATCTGCC
DELTAEF1_01	-176	+	0.958	11	TCCCACCTTCC
S8_01	5	-	0.992	11	GAGGCAATTAT
MZF1_01	16	-	0.986	8	AGAGGGGA
				_	

# Promoter sequence P29B6 (555 bp):

Matrix	Position	Orientation	Score	Length	Sequence
ARNT_01	-311	+	0.964	16	GGACTCACGTGCTGCT
NMYC_01	-309	+	0.965	12	ACTCACGTGCTG
USF_01	-309	+	0.985	12	ACTCACGTGCTG
USF_01	-309	-	0.985	12	CAGCACGTGAGT
NMYC_01	-309	-	0.956	12	CAGCACGTGAGT
MYCMAX_02	-309	•	0.972	12	CAGCACGTGAGT
USF_C	-307	+	0.997	8	TCACGTGC
USF_C	-307	-	0.991	8	GCACGTGA
MZF1_01	-292	-	0.968	8	CATGGGGA
ELK1_02	-105	+	0.963	14	CTCTCCGGAAGCCT
CETS1P54_01	-102	+	0.974	10	TCCGGAAGCC
AP1_Q4	-42	-	0.963	11	AGTGACTGAAC
AP1FJ_Q2	-42	•	0.961	11	AGTGACTGAAC
PADS_C	45	+	1.000	9	TGTGGTCTC

Figure 9





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100.0% identity in 125 aa overlap

 SEQ ID NO: 217
 LVKPEKTKAVENYLIQMARYGQLSEKVSEQGLIEILKKVSQQTEKTTTVKFNRRKVMDSD

 SEQ ID NO: 516
 LVKPEKTKAVENYLIQMARYGQLSEKVSEQGLIEILKKVSQQTEKTTTVKFNRRKVMDSD

 70
 80
 90
 100
 110
 120

SEQ ID NO: 217 EDDDY ::::X SEQ ID NO: 516 EDDDY

------

FIGURE 10





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# CLUSTAL W(1.5) multiple sequence alignment

SEQ SEQ	ID ID	NO: NO:	517 232 174 175	MFCPLKLILLPVLLDYSLGLNDLNVSPPELTVHVGDSALMGCVFQSTEDKCIFKIDWTLS
SEQ SEQ	ID ID	NO:	517 232 174 175	PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDNLCNDGSLLLQDVQDVE PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDILCNDGSLLLQDVQEADQGTYICEIRL PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDNLCNDGSLLLQDVQEADQGTYICEIRL PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDILCNDGSLLLQDVQEADQGTYICEIRL
SEQ SEQ SEQ	ID :	NO: NO:	232 174	KGESQVFKKAVVLHVLPEEPKGTQMLTKGESQVFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVEWIFSGRRAKEEKGESQVFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVEWIFSGRRAK
SEQ SEQ SEQ	ID I	NO:	232 174	IVFRYYHKLRMSAEYSQSWGHFQNRVNLVGDIFRNDGSIMLQGVRESDGGNYTCSIHLGN VTRRKHHCVREGSG
SEQ SEQ SEQ	ID N	: 07/ : 07/	232 174	LVFKKTIVLHVSPEEPRTLVTPAALRPLVLGGNQLVIIVGIVCATILLLPVLILIVKKTC
SEQ SEQ SEQ	ID N	10 :	232 174	GNKSSVNSTVLVKNTKKTNP



### 12/15

99.6% identity in 225 aa overlap SEQ ID NO: 515 PTAVQKEEARQDVEALLSRTVRTQILTGKELRVATQEKEGSSGRCMLTLLGLSFILAGLI SEQ ID NO: 231 LRVATQEKEGSSGRCMLTLLGLSFILAGLI SEQ ID NO: 515 VGGACIYKYFMPKSTIYRGEMCFFDSEDPANSLRGGEPNFLPVTEEADIREDDNIAIIDV SEQ ID NO: 231 VGGACIYKYFMPKSTIYRGEMCFFDSEDPANSLRGGEPNFLPVTEEADIREDDNIAIIDV SEQ ID NO: 515 PVPSFSDSDPAAIIHDFEKGMTAYLDLLLGNCYLMPLNTSIVMPPKNLVELFGKLASGRY SEQ ID NO: 231 PVPSFSDSDPAAIIHDFEKGMTAYLDLLLGICYLMPLNTSIVMPPKNLVELFGKLASGRY SEQ ID NO: 515 LPQTYVVREDLVAVEEIRDVSNLGIFIYQLCNNRKSFRLRRRDLLLGFNKRAIDKCWKIR SEQ ID NO: 231 LPQTYVVREDLVAVEEIRDVSNLGIFIYQLCNNRKSFRLRRRDLLLGFNKRAIDKCWKIR SEQ ID NO: 515 HFPNEFIVETKICQE :::::::::::::::: SEQ ID NO: 231 HFPNEFIVETKICQE





### 13/15

99.7% identity in 353 aa overlap SEQ ID NO:196 MERGLKSADPRDGTGYTGWAGIAVLYLHLY SEQ ID NO:518 LAEGYFDAAGRLTPEFSQRLTNKIRELLQQMERGLKSADPRDGTGYTGWAGIAVLYLHLY SEQ ID NO:196 DVFGDPAYLQLAHGYVKQSLNCLTKRSITFLCGDAGPLAVAAVLYHKMNNEKQAEDCITR SEQ ID NO:518 DVFGDPAYLQLAHGYVKQSLNCLTKRSITFLCGDAGPLAVAAVLYHKMNNEKQAEDCITR SEQ ID NO:196 LIHLNKIDPHAPNEMLYGRIGYIYALLFVNKNFGVEKTPQSHIQQICETILTSGENLARK SEQ ID NO:518 LIHLNKIDPHAPNEMLYGRIGYIYALLFVNKNFGVEKIPQSHIQQICETILTSGENLARK SEQ ID NO:196 RNFTAKSPLMYEWYQEYYVGAAHGLAGIYYYLMQPSLQVSQGKLHSLVKPSVDYVCQLKF SEQ ID NO:518 RNFTAKSPLMYEWYQEYYVGAAHGLAGIYYYLMQPSLQVSQGKLHSLVKPSVDYVCQLKF SEQ ID NO:196 PSGNYPPCIGDNRDLLVHWCHGAPGVIYMLIQAYKVFREEKYLCDAYQCADVIWQYGLLK SEQ ID NO:518 PSGNYPPCIGDNRDLLVHWCHGAPGVIYMLIQAYKVFREEKYLCDAYQCADVIWQYGLLK SEQ ID NO:196 KGYGLCHGSAGNAYAFLTLYNLTQDMKYLYRACKFAEWCLEYGEHGCRTPDTPFSLFEGM SEQ ID NO:518 KGYGLCHGSAGNAYAFLTLYNLTQDMKYLYRACKFAEWCLEYGEHGCRTPDTPFSLFEGM SEQ ID NO:196 AGTIYFLADLLVPTKARFPAFEL SEQ ID NO:518 AGTIYFLADLLVPTKARFPAFEL





#### 14/15

98.5% identity in 194 aa overlap SEQ ID NO:519 ARNLPPLTDAQKNKLRHLSVVTLAAKVKCIPYAVLLEALALRNVRQLEDLVIEAVYADVL SEQ ID NO:158 ARNLPPLTEAQKNKLRHLSVVTLAAKVKCIPYAVLLEALALRNVRQLEDLVIEAVYADVL SEQ ID NO:519 RGSLDQRNQRLEVDYSIGRDIQRQDLSAIAQTLQEWCVGCEVVLSGIEEQVSRANQHKEQ SEQ ID NO:158 RGSLDQRNQRLEVDYSIGRDIQRQDLSAIARTLQEWCVGCEVVLSGIEEQVSRANQHKEQ SEQ ID NO:519 QLGLKQQIESEVANLKKTIKVTTAAAAAATSQDPEQHLTELREPASGTNQRQPSKKASKG SEQ ID NO:158 QLGLKQQIESEVANLKKTIKVTTAAAAAATSQDPEQHLTELREPAPGTNQRQPSKKASKG SEQ ID NO:519 KGLRGSAKIWSKSN SEQ ID NO:158 KGLRGSAKIWSKSN 88.7% identity in 62 aa overlap SEQ ID NO:519 MSAEVKVTGQNQEQFLLLAKSAKGAALATLIHQVLEAPGVYVFGELLDMPNVRELAESDF SEQ ID NO:158 MSAEVKVTGQNQEQFLLLAKSAKGAALATLIHQVLEAPGVYVFGELLDMPNVRELXARNL 

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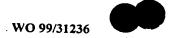
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15/15

68.9% identity in 74 aa overlap

10 20 30 40 50

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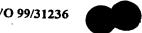
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                               Met Lys Lys Val Leu Leu Leu Ile
                                       -15
aca gcc atc ttg gca gtg gct gtw ggt ttc cca gtc tct caa gac cag
                                                                  161
Thr_Ala_Ile_Leu_Ala_Val_Ala_Val_Gly_Phe_Pro_Val_Ser_Gln_Asp_Gln
               -5
gaa cga gaa aaa aga agt atc agt gac agc gat gaa tta gct tca ggr
                                                                  209
Glu Arg Glu Lys Arg Ser Ile Ser Asp Ser Asp Glu Leu Ala Ser Gly
                           15
                                              20
with the geg tec con tac con tat con the ego con cet con con att
                                                                  257
Xaa Phe Val Phe Pro Tyr Pro Tyr Pro Phe Arg Pro Leu Pro Pro Ile
                       30
                                          35
cca ttt cca aga ttt cca tgg ttt aga cgt aan ttt cct att cca ata
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Pro Phe Pro Arg Phe Pro Trp Phe Arg Arg Xaa Phe Pro Ile Pro Ile
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                                      50
cct gaa tct gcc cct aca act ccc ctt cct agc gaa aag taaacaaraa
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Pro Glu Ser Ala Pro Thr Thr Pro Leu Pro Ser Glu Lys
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			a agaato										
			t tcctgt										
aagact	taaca tt	ttgtgaa	g ttgtaa	ıaaca	gaa	aacc	tgt	taga			-	_	
									Me	-2	-	p Phe	!
cag ca	aa ggc c	tc agt	ttc ctt	cct	tca	acc	ctt	gta	att	_		tct	405
_		_	Phe Leu			_		_					
	-15			-10					-5				
gct go	ct ttc a	ta ttt	tca tac	att	act	gca	gta	aca	ctc	cac	cat	ata	453
Ala Al	la Phe I	le Phe	Ser Tyr	Ile	Thr	Ala	Val	Thr	Leu	His	His	Ile	
1			5				10					15	
			tat atc										501
Asp Pi	ro Ala L		Tyr Ile	Ser	Asp		Gly	Thr	Val	Ala		Xaa	
aaa to	ar tto t	20 tt ggg	gca atg	cta	2 <b>2</b> +	25	~~~	<b>ac</b> -	a++	++-	30	C22	549
			Ala Met										347
-,,		5	1106		40		a	~~ a	· a ·	45	Cys		
aaa ta	_	-	taatt ca			, aak	ttca	ttt	cato		aaa		602
Lys									_				
ctctt	caraa ac	atgtctt	t acaago	atat	cto	ttgt	att	gctt	tcta	ca	tgtt	gaatt	662



gtctggcaat atttctgcag tggaaaattt gatttarmta gttcttgact gataaatatg 722 gtaaggtggg cttttccccc tgtgtaattg gctactatgt cttactgagc caagttgtaw 782 tttgaaataa aatgatatga gagtgacaca aaaaaaaaa 822

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Leu Ser Pro Cys Leu Thr Ala Pro Xaa Ser Pro Arg Leu Ala Met Met 

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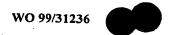
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cooggagata ggaccaacog toaggaatgo gaggaatgot totottogga cootatogag	180
gcacacagac agacc atg ggg att ctg tct aca gtg aca gcc tta aca ttt	231
Met Gly Ile Leu Ser Thr Val Thr Ala Leu Thr Phe	
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Ala Xaa Ala Leu Asp Gly Cys Arg Asn Gly Ile Ala His Pro Ala Ser	
1 5 10	
gag aag cac aga ctc gag aaa tgt agg gaa ctc gag asc asc cac tcg	327
Glu Lys His Arg Leu Glu Lys Cys Arg Glu Leu Glu Xaa Xaa His Ser	
15 20 25 25 25 26 26 26 26 26 26 26 26 26 26 26 26 26	375
gcc cca gga tca acc cas cac cga aga aaa aca acc aga aga aat tat Ala Pro Gly Ser Thr Xaa His Arg Arg Lys Thr Thr Arg Arg Asn Tyr	5/3
30 35 40 45	
tot toa goo tgaaatgaak cogggatoaa atggttgotg atcaragece	424
Ser Ser Ala	
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Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln Cys Phe Lys
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Glu Gly Arg Trp Ala Leu Xaa Gly Gly Leu Leu Leu Gln Asp Pro Ser
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                                       110
agg ggc ara aaa acc tgg gtg cgg cca cag ctg ggg ctc cca ctc tgc
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Arg Gly Xaa Lys Thr Trp Val Arg Pro Gln Leu Gly Leu Pro Leu Cys
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436



95

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Ala Phe Lys Val Arg Leu Ser Ile Arg Thr Ala Leu Gly Asp Lys Ala 10 20 25
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Tyr Ala Trp Asp Thr Asn Glu Glu Tyr Leu Phe Lys Ala Met Val Ala 30 35 40
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60 65 70 aca gac cct tca aaa aat cac acc ctt cct gct gtt gag gtg caa tca 340
Thr Asp Pro Ser Lys Asn His Thr Leu Pro Ala Val Glu Val Gln Ser 75 80 85
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100

gac caa act ctg gaa ttt tta aaa atc cct tcc aca ctt gca cca ccc Asp Gln Thr Leu Glu Phe Leu Lys Ile Pro Ser Thr Leu Ala Pro Pro



Met	Asp	PIO	125	Val	Pro	Ile	Trp	Ile 130	Ile	Ile	Phe	Gly	Val	Ile		484
СуБ	116	140	TTE	vaı	Ala	Ile	Ala 145	Leu	Leu	Ile	Leu	Ser	999 999	Ile		532
GIII	155	Add	лаа	гÀг	Asn	Lys 160	Glu	Pro	tct Ser	Glu	Val	Asp	Asp	Ala	Glu	580
rat Xaa	aak Xaa	Cys	gaa Glu	aac Asn	atg Met	atc	aca Thr	att	gaa Glu	aat	ggc	atc	ccc	tct	gat	628
1/0					175					180					185	
PIO	теп	Asp	Met	Lys 190	Gly	Gly	His	Ile	aat Asn 195	Asp	Ala	Phe	Met	Thr	Glu	676
Asp	GIU	Arg	205	Thr	Pro	Leu			tg t	•						727
atta wttt c	aaca tgtt	tt t tc a	gttt ccat	ctgt	g tg c tt	actg ttgt	ctga aata	gca aat	tcct	gaa aat	atac gtgc	caag ttga	ag c aa a	agat aaaa	catat aaaaa	787 847 848

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26

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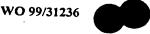
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                                                            120
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gcc ctc ctc ctg cct cac tgc cag aag ccc ttt gtg tat gac ctt cac Ala Leu Leu Leu Pro His Cys Gln Lys Pro Phe Val Tyr Asp Leu His 1 5 10 15	144
gca gtc aag aac gac ttc cag att tgg agg ttg ata tgt gga aga ata Ala Val Lys Asn Asp Phe Gln Ile Trp Arg Leu Ile Cys Gly Arg Ile 20 25 30	192
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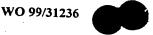
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60

55

35

50



				-													· •
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Pro S	ser	GIÀ	Leu	Ile 100	Phe	Cys	Cys	Ala	Phe 105	Cys	Ser	Glu	Thr	Lys 110	Leu	43	2
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ggc gcc gcc ttc tat ccc atc tac ttc cgg ccc cta atg aga ttg gag Gly Ala Ala Phe Tyr Pro Ile Tyr Phe Arg Pro Leu Met Arg Leu Glu 1 5 10	152
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Arg	Ala	Ser	Leu	Leu 75	Glu	act Thr	Gln	Met	Glu 80	Glu	Asp	Ile	Leu	Gln 85	Leu		340
Gin	Ala	GIu	Ala 90	Thr	Ala	gag Glu	Val	Leu 95	Gly	Glu	Val	Ala	Gln 100	Ala	Gln		388
Lys	Val	Leu 105	Arg	Asp	Ser	gtg Val	Gln 110	Arg	Leu	Glu	Val	Gln 115	Leu	Arg	Ser		436
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cag Gln	gag Glu	aga Arg	ctc Leu 170	cac His	aca Thr	gcg Ala	gcg Ala	ctc Leu 175	cca Pro	gcc Ala	tgaa	tctg	cc t	ggat	ggaac	•	533
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WO 99/31236	

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							Ile					Ser		Ser		
~~~	250		+ = +	~+~			-25					-20				4.05
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GIÀ	-15	ьeu	ser	vai	TIE	-10	Val	Met	Leu	Ala	Pro	Phe	Thr	Ala	GIA	
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1				5				-	10	2		2		15		
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Ser	Ala	Glu	Leu	Thr	Ala	Ser	Arg	Leu	Thr	Ala	Thr	Ser	Thr	Asp	Gln	
		35					40					45				
ttg	gag	gca	tta	agg	gac	att	ctg	cat	gac	atc	aca	ccc	aat	gtg	ctt	677
Leu		Ala	Leu	Arg	Asp		Leu	His	Asp	Ile	Thr	Pro	Asn	Val	Leu	
	50					55					60					
tcc	ttt	gca	ctt	gat	ttt	gac	gaa	gcc	aca	aaa	atg	att	gcg	aat	gat	725
	Phe	Ala	Leu	Asp		Asp	Glu	Ala	Thr		Met	Ile	Ala	Asn		
65	ـ				70					75					80	
gre	cat	aca	CEC	agg	aga	TCT	aaa	gcc	act	gtt	gga	cgc	cct	ttg	att	773
vai	HIS	Inr	геп		Arg	ser	гàг	Ala		vaı	GIŻ	Arg	Pro	Leu	Ile	
act	+~~	~~~	+ > +	85					90					95		001
712	£22	Dra	Tree	yra Val	Dro	TIA	200	get	gee	gag	aca mb	ctg	aga	aca Thr	cgt	821
AIG	тъ	Arg	100	vaı	PIO	116	ASII	105	vaı	GIU	Inr	Leu		THE	Arg	
aaa	acc	ccc			-+-	a+~	200		a+ -	~~~			110	~~~		960
6J A	Δla	Pro	Thr	Ara	Tla	yey Val	Ara	Lve	yea Val	Mla	720	Aac Acn	Ten	ggc Gly	Luc	869
<b>-</b> 1	2124	115		AT 9	110	Val	120	шys	vai	AIG	Arg	125	Tierr	Gry	пуъ	
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	130		2			135					140			•	<b></b>	
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Asp	Ser	Leu	Asp	Leu	His	Lys	Gly	Glu	Lys	Ser	Glu	Ser	Ala	Glu	Leu	
145			_		150	_	_		_	155					160	
ctg	agg	cag	tgg	gct	cag	gag	ctg	gag	gag	aat	ctc	aat	gag	ctc	acc	1013
Leu	Arg	Gln	Trp	Ala	Gln	Glu	Leu	Glu	Glu	Asn	Leu	Asn	Glu	Leu	Thr	
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cat	atc	cat	cag	agt	cta	aaa	gca	ggc	tagg	ccca	at t	gttg	cggg	ga		1060
His	Ile	His		Ser	Leu	Lys	Ala	_								
			180					185								
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															cctgt	1180
															cccca	1240
															tgtag	1300 1360
															acage	1420
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atto	atac	ac t	ccct	cccc	t tt	tgga	agto	cct	aata	aaa	actt	gctg	gt t	ttgc	agctt	1960
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                                                                      240
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                                                                      300
tactcctcat ctgtgtaatg aaacagagca tgagtgggaa aaagttaaga gatatttaaa
                                                                      360
aggicatact agaaatitat cittggatat tgcaaagcta aaggaacaag tatticaagc
                                                                      420
                                                                      472
ccctcagata catctgacac ta atg cca gga act gaa gtg ctt gaa gga gct
                         Met Pro Gly Thr Glu Val Leu Glu Gly Ala
aca gac gga tta gca gct att aac ctg cta aaa tgg atc aag aca ctt
                                                                      520
Thr Asp Gly Leu Ala Ala Ile Asn Leu Leu Lys Trp Ile Lys Thr Leu
                                    -30
                -35
gga ggc tct gtg att tca atg att gtg ctt tta atc tgt gtt gtt tgt
Gly Gly Ser Val Ile Ser Met Ile Val Leu Leu Ile Cys Val Val Cys
            -20
                                 -15
                                                     -10
ctt tat ata gtc tgt aga tgc gga agc cac ctc tgg aga gaa agc cac
                                                                      616
Leu Tyr Ile Val Cys Arg Cys Gly Ser His Leu Trp Arg Glu Ser His
                                                                      669
cac tgagagcaag caatgatagc tgtggcggtt ttgcaaaaag aaaagggaga
His
                                                                      729
caagcgccca gctatagtta ccaataaagc atggtactgg tattaaaata ggcatgtgtt
                                                                      789
ctgttccaat ggaacagaat agagaaccca gaaacaaagc caaatattta cagccaactg
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                                                                      909
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tatacaaaaa tcaactcaaa atgggtcaaa gtcttaactc taagacctga aaccataaca
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attctagaaa ataacattgg aaaaactctt ctagacattg gtttaggcaa aaagttcatg
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accaagaacc caaaagcaaa tgcaataaaa aggaagataa atagatggga cctaattaag
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ctgaaaagct tctgcatagc aaaaggaata atcagcagag caaacagaca acccacaggg
                                                                     1149
tgggagaaaa tatttqcaag ctatgtatct gacaatggac taatatccag aatctacaag
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	Me	et Cys Ile Ser	Gly Leu Cys Gln Ile	е
	1		5	
gtt ggc tgc gat	cac cag ctg gg	ga age ace gte	aag gaa gat aac tg	280
Val Gly Cys Asp	His Gln Leu Gl	ly Ser Thr Val	Lys Glu Asp Asn Cy	S
10	15	20	25	
ggg gtc tgc aac	gga gat ggg to	cc acc tgc cgg	ctg gtc cga ggg cag	328
			Leu Val Arg Gly Gli	
	30	35	40	
tat aaa too cag	ctc tcc gca ac	cc aaa tco gat	gat act gtg gtt gca	a 376
			Asp Thr Val Val Ala	
45		50	- 55	
			tta aaa ggt cct gat	
Ile Pro Tyr Gly !	Ser Arg His Il	le Arg Leu Val	Leu Lys Gly Pro Asp	þ
60	65	5	70	
cac tta tat ctg	gaa acc aaa ac	c ctc cag ggg	act aaa ggt gaa aad	472
His Leu Tyr Leu (	Glu Thr Lys Th	r Leu Gln Gly	Thr Lys Gly Glu Ass	n.
75	80	-	85	
agt ctc agc tcc a	aca qqa act tt	c ctt gtg gac	aat tot agt gtg gad	520
			Asn Ser Ser Val Ası	
90	95	100	105	
tto cag aga ttt			atg gct gga cca cto	
			Met Ala Gly Pro Let	
	110 ASP BYS G1 110	115	120	4
· · · · · · · · · · · · · · · · · · ·				
			ggc tcc gct gac agt	
1MI AIA ASP PNE . 125	ile val Lys il	e arg asn ser	Gly Ser Ala Asp Ser 135	<b>5</b>
aca gtc cag ttc a	atc ttc tat ca	a ccc atc atc	cac cga tgg agg gag	g 664
Thr Val Gln Phe	Ile Phe Tyr Gl	n Pro Ile Ile	His Arg Trp Arg Glu	1
140	14		150	
acq gat ttc ttt d	ect toc tca oc	a acc tot oga	gga ggt tat cag ctg	712
Thr Asp Phe Phe I	Pro Cvs Ser Al	a Thr Cvs Glv	Gly Gly Tyr Gln Let	,
155	160	J UJU ULY	165	•
aca tcg gct gag t		ת פתת פתר פפת		747
Thr Ser Ala Glu (			~3	(#/
170				
170	175	180		

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	PCT/IB98/02122

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ctg ccc ttc ccc gtg ctc ctt ctg gcc gct ctg cct ccg gtg ctg c	101												
cct ggg gcg gcc ggc ttc aca cct tcc ctc gat agc gac ttc acc ttt Pro Gly Ala Ala Gly Phe Thr Pro Ser Leu Asp Ser Asp Phe Thr Phe 1 5 10 15	149												
acc ctt ccc gcc ggc cag aag gag tgc ttc tac cag ccc atg ccc ctg Thr Leu Pro Ala Gly Gln Lys Glu Cys Phe Tyr Gln Pro Met Pro Leu 20 25 30	197												
aag gcc tcg ctg gag atc gag tac caa gtt tta gat gga gca gga tta Lys Ala Ser Leu Glu Ile Glu Tyr Gln Val Leu Asp Gly Ala Gly Leu 35 40 45	245												
gat att gat ttc cat ctt gcc tct cca gaa ggc aaa acc tta gtt ttt Asp Ile Asp Phe His Leu Ala Ser Pro Glu Gly Lys Thr Leu Val Phe . 50 55 60	293												
gaa caa aga aaa tca gat gga gtt cac act gta gag act gaa gtt ggt Glu Gln Arg Lys Ser Asp Gly Val His Thr Val Glu Thr Glu Val Gly 65 70 75	341												
gat tac atg ttc tgc ttt gac aat aca ttc agc acc att tct gag aag Asp Tyr Met Phe Cys Phe Asp Asn Thr Phe Ser Thr Ile Ser Glu Lys 80 85 90 95	389												
gtg att ttc ttt gaa tta atc ccg gat aat atg gga gaa cag gca caa Val Ile Phe Phe Glu Leu Ile Pro Asp Asn Met Gly Glu Gln Ala Gln 100 105 110	437												
gaa caa gaa gat tgg aag aaa tat att act ggc aca gat ata ttg gat Glu Gln Glu Asp Trp Lys Lys Tyr Ile Thr Gly Thr Asp Ile Leu Asp 115 120 125	485												
atg aaa ctg gaa gac atc ctg gtc agt atg gtc ttc taataaaata Met Lys Leu Glu Asp Ile Leu Val Ser Met Val Phe 130 135	531												
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<211> 370

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<222> 357..370

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taggagaagg gcatgctcag gccagcccat tagcccagga ggaggacaag aaacacacgg	171
agcagacaca agccacctca ccaacccagc caaggctgtc ctgaattagc aaccctgaca	231
cgtgtgagca agtccaacgg acaccggaag atccacctag tcaagcccaa ccaagactgg	291
cagagetgec aagetgacea ettaaggege atgaggaata aacaetegtt getgeatgee	351
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tgg aag gac aag gtt gtt gac ctc ctg tac tgg aga gac att aag aag
                                                                      103
Trp Lys Asp Lys Val Val Asp Leu Leu Tyr Trp Arg Asp Ile Lys Lys
                    -30
                                         -25
act gga gtg gtg ttt ggt gcc agc cta ttc ctg ctg ctt tca ttg aca
                                                                      151
Thr Gly Val Val Phe Gly Ala Ser Leu Phe Leu Leu Ser Leu Thr
                -15
                                    -10
gta ttc agc att gtg agc gta aca gcc tac att gcc ttg gcc ctg ctc
                                                                      199
Val Phe Ser Ile Val Ser Val Thr Ala Tyr Ile Ala Leu Ala Leu Leu
tot gtg acc atc agc ttt agg ata tac aag ggt gtg atc caa gct atc
                                                                      247
Ser Val Thr Ile Ser Phe Arg Ile Tyr Lys Gly Val Ile Gln Ala Ile
                        20
                                             25
cag aaa tca gat gaa ggc cac cca ttc agg gca tat ctg gaa tct gaa
                                                                      295
Gln Lys Ser Asp Glu Gly His Pro Phe Arg Ala Tyr Leu Glu Ser Glu
                    35
                                         40
                                                                      343
gtt gct ata tct gag gag ttg gtt cag aag tac agt aat tct gct ctt
Val Ala Ile Ser Glu Glu Leu Val Gln Lys Tyr Ser Asn Ser Ala Leu
                                    55
                50
                                                                      391
ggt cat gtg aac tgc acg ata aag gaa ctc agg cgc ctc ttc tta gtt
Gly His Val Asn Cys Thr Ile Lys Glu Leu Arg Arg Leu Phe Leu Val
            65
                                70
gat gat tta gtt gat tct ctg aag ttt gca gtg ttg atg tgg gta ttt
                                                                      439
Asp Asp Leu Val Asp Ser Leu Lys Phe Ala Val Leu Met Trp Val Phe
                            85
acc tat gtt ggt gcc ttg ttt aat ggt ctg aca cta ctg att ttg gct
                                                                      487
Thr Tyr Val Gly Ala Leu Phe Asn Gly Leu Thr Leu Leu Ile Leu Ala
    95
                        100
etc att tea etc tte agt gtt eet gtt att tat gaa egg eat eag gea
                                                                      535
Leu Ile Ser Leu Phe Ser Val Pro Val Ile Tyr Glu Arg His Gln Ala
                    115
                                         120
cag ata gat cat tat cta gta ctt gca aat aag aat gtt aaa gat gct
                                                                      583
Gln Ile Asp His Tyr Leu Val Leu Ala Asn Lys Asn Val Lys Asp Ala
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                                     135
atg gct aaa atc caa gca aaa atc cct gga ttg aag cgc aaa gct gaa
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acgggggagg	gtcagggaag	aacgaacctt	gacgttgcag	tgcagtttca	cagatogttg	751
		atgcactgtt				811
		ttgtaagctg				871
		cactggtgga				931
		ggcaagttgc				991
aaa						994

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                                                                      120
gtcactgaga gacgtctcag agaggctgtg cagctgctgg aggactataa gcatgggacc
                                                                      180
ctgcgcccgg gggtcaccaa tgaacagctc tggagtgcac agaaaatcaa gcaggctatt
                                                                      240
ctacatccgg acaccaatga gaagatcttc atg cca ttt aga atg tca ggt tat
                                                                      294
                                 Met Pro Phe Arg Met Ser Gly Tyr
att cct ttt ggg acg cca att gta agt gtt acc ttc aaa gga ttt cct
                                                                      342
Ile Pro Phe Gly Thr Pro Ile Val Ser Val Thr Phe Lys Gly Phe Pro
                        15
ttt cta aaa aat tat ttt aaa tgt cta act tta tgt tat tgc tca cgg
                                                                      390
Phe Leu Lys Asn Tyr Phe Lys Cys Leu Thr Leu Cys Tyr Cys Ser Arg
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                                                             40
gta ttt gac tgaattgttg att
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Val Phe Asp
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Gly	Lys	Gln	Arg	Asp	Phe	Gln	Val	Arg	Ala	Ala	Pro	Gly	Trp	Asp	His		
			-30					-25					-20				
ttg	gcc	tcc	ttt	cct	ggc	cct	tct	ctc	cgg	ctg	ttt	tct	999	agt	cag		210
Leu	Ala	Ser	Phe	Pro	Gly	Pro	Ser	Leu	Arg	Leu	Phe	Ser	Gly	Ser	Gln		
		-15					-10					-5					
gcg	agt	gtc	tgt	agt	ctc	tgc	tcg	ggg	ttt	999	gct	cag	gaa				252
Ala	Ser	Val	Cys	Ser	Leu	Cys	Ser	Gly	Phe	Gly	Ala	Gln	Glu				
	1				5					10							
tgat	gtca	itg (	ctcca	acag	gt to	ggatt	ctat	tag	gctta	aagg	agga	aggga	aaa	cagco	caat	tt	312
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ctct	aaaa	ag	catca	attt	:a c1	tttta	attta	a gca	acaaa	aggc	acag	ggata	att '	ttta	cagg	aa	432
gaat	cttt	ta 1	tatg	gaaaa	aa to	ctgag	gttaa	a cat	cact	ccc	gtgg	gtgtt	tg	tagti	tctt	ac	492
aggg	gaaac	ctc (	cagt	geett	t to	gagco	egett	gtt	cgt	ccta	gtga	acad	ctg	tctgi	tttt	gt	552
ctct	tggt	gc	tgcta	atgto	ct ga	acct	gtaat	999	gagaa	aaaa	aaga	aa					597

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10



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aagcacttag	tctaatgcta	actgcaagag	gaggtgctca	gtggatgttt	agccgatacg	600
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aaccatttca	tgaatatggt	ttggaagatg	tttagtcttg	aatataatgc	gaaatagaat	720
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                                 Met Arg Gln Lys Arg Lys Gly Asp
ctc agc cct gct aag ctg atg ctg act ata gga gat gtt att aaa
                                                                      102
Leu Ser Pro Ala Lys Leu Met Met Leu Thr Ile Gly Asp Val Ile Lys
                        15
caa ctg att gaa gcc cac gag cag ggg aaa gac atc gat cta aat aag
                                                                      150
Gln Leu Ile Glu Ala His Glu Gln Gly Lys Asp Ile Asp Leu Asn Lys
gtg aga acc aag aca gct gcc aaa tat ggc ctt tct gcc cag ccc cgc
                                                                      198
Val Arg Thr Lys Thr Ala Ala Lys Tyr Gly Leu Ser Ala Gln Pro Arg
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Leu Val Asp Ile Ile Ala Ala Val Pro Pro Glu
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acaggcatga gccaccgctc cgggcctttg attttttaag gtggattttg gttgttataa
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atggagaaag gtaagagttc aagttcaacc cgtgtgtgaa agcaaaacaa tggaaaacag
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gattggcttc ttcaaaggct cctcttgtag aactgcctct ttgaaatttc gaggtaatct
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actitiggaga ctctgcctgg agagggtcag ttcctaagtt aaaagcatcg cttaaccttg
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cgg aaa ata cag cgt ttc ttg tct cag cca ttc cag gtt gct gag gtc Arg Lys Ile Gln Arg Phe Leu Ser Gln Pro Phe Gln Val Ala Glu Val 20 25 30	397
	445
	493
	541
	595
ctccttgccc ctaacccaaa aagcttcatt tttctgtgta ggctgcacaa gagccttgat tgaagatata ttctttctga acagtattta aggtttccaa taaagtgtac acccctcaaa	655 715 725
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gtg atg agt gcg gaa gtg aag gtg aca ggg cag aac cag gag caa ttt Met Ser Ala Glu Val Lys Val Thr Gly Gln Asn Gln Glu Gln Phe

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Asp	Met	Pro		Val	Arg	Glu	Leu		Ala	Arg	Asn	Leu		Pro	Leu		
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пуъ	пур	THE	110	пуs	vai	Inr	Inr	115	Ala	Ата	Ala	Ата	120	THE	Sei		
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Thr		Gln	Arg	Gln	Pro		Lys	Lys	Ala	Ser		Gly	Lys	Gly	Leu		
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PCT/IB98/02122
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Thr Tyr Asn Lys His Ile Asn Ile Ser Phe His Arg
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ccqtaaggga gaaagagatc ttcccaatca gcaatcaccg taaaagcctg ctgtgttccc
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Thr	Tyr		Lys	His	Ile	Asn		Ser	Phe	His	Arg	Phe	Pro	Leu	Asp	
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	aaa															266
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	cca															314
Val	Pro	Gly	Lys	His	Thr	Phe	Leu	Cys	Ser	Lys	His	Phe	Glu	Ala	Ser	
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Cys	Phe	Asp	Leu	Thr	Gly	Gln	Thr	Arg	Arg	Leu	Lys	Met	Asp	Ala	Val	
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	Thr															
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His	Met	Leu	Pro	Thr	Ala	Leu	Ser	Ser	Leu	Pro	Leu	Glu	Asp	Phe	Lys	
	190					195					200		-		=	
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	Leu															
205				•	210		•			215					220	
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Lvs	Gln	Thr	Lvs	Ser	Thr	Phe	Tle			.50	, ,	·cugo	.9 00	. cga	.9000	010
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aata	aaact	++ +	2011	.cayo	.a yl	ratt	2010		++~+	act	-aug	tas	taa t		gaata	908 968
aaaa	10066 10066	.ca t	4+++	adal		altt	yaaa	atg	agtg	yaa	gcgc	CLT	ca t	.caga	attac	1028
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Trp Phe Val His Ser Ser Ala Leu Gly	Leu Val Leu Ala Pro Pro Phe
-10 -5	1
tcc tct ccg ggc act gac ccc acc ttt	ccg tgt att tac tgt agg cta 149
Ser Ser Pro Gly Thr Asp Pro Thr Phe	Pro Cys Ile Tyr Cys Arg Leu
5 10	15
tta aat atg atc atg acc cgc ctt gca	ttt tca ttc atc acc tgt tta 197
Leu Asn Met Ile Met Thr Arg Leu Ala	Phe Ser Phe Ile Thr Cys Leu
20 25	30 35
tgc cca aat tta aag gaa gtt tgt ctc	att ttg cca gaa aaa aat tgt 245
Cys Pro Asn Leu Lys Glu Val Cys Leu	
40	45 50
aat agt cgg cac gct gga ttt gta ggg	cca gca aaa ttg cgg cag 290
Asn Ser Arg His Ala Gly Phe Val Gly	Pro Ala Lys Leu Arg Gln
55 60	65
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atttgatect tggttectat ttegatecte et	ttggaatc tgaaaatcgg tctccatgtt 410
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gcttttaact tcttctttga tctaaggatt acctacttgt taatttccaa atattatctt	420
atctatctat ctatctatct atctatctat ctatctat	480
gget atg teg eeg agg etg gag tge agt ggt gea ate ttg get eac tge	529
Met Ser Pro Arg Leu Glu Cys Ser Gly Ala Ile Leu Ala His Cys	
1 5 10 15	
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aac ccc cgc ctc cca ggt tca agt tat tct cct gcc tca gct act tgg Asn Pro Arg Leu Pro Gly Ser Ser Tyr Ser Pro Ala Ser Ala Thr Trp	577
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Asn Pro Arg Leu Pro Gly Ser Ser Tyr Ser Pro Ala Ser Ala Thr Trp	577 626
Asn Pro Arg Leu Pro Gly Ser Ser Tyr Ser Pro Ala Ser Ala Thr Trp 20 25 30	
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Gln Asn Val Ile Asn Thr Val Lys Gly Lys Ala Leu Glu Val Ala Glu
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                                                                      152
tac ctg acc ccg gtc ctc aag gaa tca aag ttt agg gaa aca ggt gta
Tyr Leu Thr Pro Val Leu Lys Glu Ser Lys Phe Arg Glu Thr Gly Val
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Ile Thr Pro Glu Glu Phe Val Ala Ala Gly Asp His Leu Val His His
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                    -20
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Cys Pro Thr Trp Gln Trp Ala Thr Gly Glu Glu Leu Lys Val Lys Ala
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Tyr Leu Pro Thr Gly Lys Gln Phe Leu Val Thr Lys Asn Val Pro Cys
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Thr Gly Ile Thr Gly Ile Thr Glu Ala Val Lys Glu Ile Thr Leu Glu
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Asn Lys Asp Asn Ile Arg Leu Gln Asp Cys Ser Ala Leu Cys Glu Glu
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Glu Glu Asp Glu Asp Glu Gly Glu Ala Ala Asp Met Glu Glu Tyr Glu
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                                                                      584
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Glu Ser Gly Leu Leu Glu Thr Asp Glu Ala Thr Leu Asp Thr Arg Lys
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Ile Val Glu Ala Cys Lys Ala Lys Thr Asp Ala Gly Glu Asp Ala
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Tyr	Gln	Thr	Pro 155	Arg	Leu	Trp	Leu	Phe 160	Gly	Tyr	Asp	Glu	Gln 165	Arg	Gln		
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Pro	Leu	Thr 170	Val	Glu	His	Met	Tyr 175	Glu	Asp	Ile	Ser	Gln 180	Asp	His	Val		
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Lys	Lys 185	Thr	Val	Thr	Ile	Glu 190	Asn	His	Pro	His	Leu 195	Pro	Pro	Pro	Pro		
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Met	Cys	Ser	Val	His		Cys	Arg	His	Ala	Glu	Val	Met	Lys	Lys			
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ьеп	Leu	тте		Leu	ьуs	Pne	vaı		Ala	vaı	TTE	Pro		Ile	GIU		
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	_			_		ttc Phe		_	Laai	-yaa	Jay d	agcai	.aaa	aL		1015	
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65

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60

290

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401

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568

538

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Leu Pro Phe Val Ser Leu Gly Leu Met Cys Phe Gly Ala Leu Ile Gly	
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Leu Cys Ala Cys Ile Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly	
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att ctc cat ctc ctt gca ggt ctg tgt aca ctg ggc tca gta agt tgt	302
Ile Leu His Leu Leu Ala Gly Leu Cys Thr Leu Gly Ser Val Ser Cys 15 20 25	
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Ala Pro Leu Gln Phe Met Ala Ser Ala Leu Phe Ile Trp Ala Ala His	
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			gtg ttc Val Phe										97	
	g Asn Pr		gtg ccc Val Pro -30										145	
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Met Se	r Gly Se 15	er Phe	cag ctg Gln Leu	Val 20	Pro	Arg	Glu	Glu	Leu 25	Pro	Arg	His	289	
Ala Hi 30	s Leu Ar	rg Phe	tac acg Tyr Thr 35	Ala	Pro	Pro	Gly	Pro 40	Arg	Leu	Ala	Leu	337	
Cys Ph 45	e Val As	sp Ile	cgc cgg Arg Arg 50	Phe	Gly	Arg	Trp 55	Asp	Leu	Gly	Gly	Lys 60	385	
Trp Gl	n Pro Gl	ly Arg 65	ggg ccc Gly Pro	Cys	Val	Leu 70	Gln	Glu	Tyr	Gln	Gln 75	Phe	433	
Arg Le	u Lys II	le Pro O	ccc ttt Pro Phe	Glu	Lys 85	Ala	Arg	Ser	Val	Leu 90	Glu	Ala	481	
Leu Gl	n Gln H: 95	is Arg	ccg agc Pro Ser	Pro 100	Glu	Leu	Thr	Leu	Ser 105	Gln	Lys	Ile	529	
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	s Lys S		gcc aca Ala Thr 195	Gln									817	



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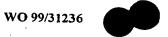
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631



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gcc Ala	ctg Leu	agg Arg	cct Pro -5	ctg Leu	gtc Val	ttg Leu	ggt Gly	ggt Gly 1	aat Asn	cag Gln	ttg Leu	gtg Val 5	atc Ile	att	gtg Val	781
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cat cac tgt gtt aga gaa ggc tct ggc tgatggtatc aggacaaagg His His Cys Val Arg Glu Gly Ser Gly 145 150	540
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								tgt Cys								193
								gac Asp								241
		_				_		ccc Pro 50			_			_	_	289
atc Ile	taat	tgaa	ac a	aaga	ctgaa	ag ga	atcaa	ataaa	a cag	gccat	ctg	ccc	ette	aaa		342
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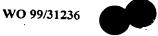
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203

233



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ctc ttc ttc ttt	ctc ttc ctc ctc a	cc agg ggc tca c	tt tct cca aca	99
Leu Phe Phe Phe 1	Leu Phe Leu Leu T	hr Arg Gly Ser L	eu Ser Pro Thr	
-10	-5	1	5	
Lvs Tvr Asn Leu 1	ttg gag ctc aag g Leu Glu Leu Lys G	ag for tgo ato o	gg aac cag gac	147
	lo	15 15	rg Asn Gin Asp 20	
tgc gag act ggc t	tgc tgc caa cgt g	ct cca gac aat to	gc gag tcg cac	195
-Cys-Glu-Thr-Gly-C	Cys Cys Gln Arg A	la Pro Asp Asn C	ys Glu Ser His	
25	3	0	35	
tgc gcg gag aag g	ggg tcc gag ggc a	gt ctg tgt caa ac	cg cag gtg ttc	243
Cys Ala Glu Lys 0	ary ser Gru Gry So			
ttt ggc caa tat a		50 Sta caa see at		201
Phe Gly Gln Tyr A	Arg Ala Cys Pro C	vs Leu Arg Asn Le	ng act tgt ata	291
55	60	65		
tat tca aag aat g	gag aaa tgg ctt ag	gc atc gcc tat go	gc cgt tgt cag	339
Tyr Ser Lys Asn G	Elu Lys Trp Leu S	er Ile Ala Tyr Gl	ly Arg Cys Gln	
70	75	80	85	
aaa att gga agg c Lys Ile Gly Arg G	ag aag ttg got aa	ag aaa atg tto tt	c tagtgeteee	388
	on the new Ara D	s Lys Met Phe Ph 95	ie	
teettettge tgeete	=		ragag ststatatts	448
accetgttcc ccagag	cctc caccatgagt o	gagggaagt ggggag	itgat tgaaataaag	508
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_	- <b>-</b>	J.J	Met	
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atc cta tgt ttc ct	tt ctt cct cat ca	t cgt ctt cag ga	a gcc aga cag	107
Ile Leu Cys Phe Le			_	
att caa gta ttg a	10		15	

att caa gta ttg aag atg ctg cca agg gaa aaa tta aga aga aga gaa

Ile Gln Val Leu Lys Met Leu Pro Arg Glu Lys Leu Arg Arg Glu 25

gag aga aaa caa ata aat ggg aaa aaa gaa agg aca aaa tat gaa aca

Glu Arg Lys Gln Ile Asn Gly Lys Lys Glu Arg Thr Lys Tyr Glu Thr .\_\_. 35. ... 45. ... 40..... 40......

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Pro Arg Lys Arg Glu Gly Lys Lys Lys

30

<210> 80 <211> 660

50

<212> DNA

650

660



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		ore				/										
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						Met	: Val	Ala	a Let	1 Asi -10		ı Ile	e Le	u Val	l Pro	
	tgc g															160
Cys	Cys 1	Ala	Ala	Trp 1	Cys	Asp	Pro	Arg 5	Arg	Ile	His	Ser	Gln 10	Asp	Asp	
ata	ccc d	cat	agc	_	act	act	gat	-	aaa	tct	aca	ato		caa	cat	208
Val	Pro A	Arg	Ser	Ser	Ala	Ala	Asp	Thr	Glv	Ser	Ala	Met	Gln	Arq	Ara	
		15					20		•			25				
gag	gcc t	gg	gct	ggt	tgg	aga	agg	tca	caa	ccc	ttc	tct	gtt	ggt	ctg	256
Glu .	Ala :	rp	Ala	Gly	Trp	Arg	Arg	Ser	Gln	Pro	Phe	Ser	Val	Gly	Leu	
	30					35					40					
	tct g															304
	Ser A	Ala	Glu	Arg		Glu	Asn	Gln	Pro	_	Lys	Leu	Ser	Trp	_	
45					50					55					60	
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Ser	Leu V	val	GIY	65	GIY	Tyr	Arg	11e	Cys	Asp	Leu					
gaag	ccac	c t	gggd	taca	g aa	acca	cagt	ctt	ccca	agca	atta	ttac	aa ·	ttctt	gaatt	410
															tccag	
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gagtacaccc tttccaggaa taatgttttg ggaaacactg aaatgaaatc ttcccagtat

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ctc	tgc	tta	CCC	aga	ccc	gaa	gca	cgt	gag	gat	ccg	atc	cca	gtt	cct	103
Leu	Cys	Leu	Pro	Arg	Pro	Glu	Ala	Arg	Glu	Asp	Pro	Ile	Pro	Val	Pro	
-55					-50					-45					-40	
cca	agg	ggc	ctg	ggt	gct	999	gag	999	tca	ggt	agt	cca	gtg	cgt	cca	151
Pro	Arg	Gly	Leu	Gly	Ala	Gly	Glu	Gly	Ser	Gly	Ser	Pro	Val	Arg	Pro	
				35					3.0				_	-25		
cct	gta	tcc	acc	tgg	ggc	cct	agc	tgg	gcc	cag	ctc	ctg	gac	agt	gtc	199
Pro	Val	Ser	Thr	Trp	Glŷ	Pro	Ser	Trp	Ala	Gln	Leu	Leu	Asp	Ser	Val	
			-20					-15					-10			
cta -	tgg	ctg	999	gca	cta	gga	ctg	aca	atc	cag	gca	gtc	ttt	tcc	acc	247
Leu	Trp	Leu	Gly	Ala	Leu	Gly	Leu	Thr	Ile	Gln	Ala	Val	Phe	Ser	Thr	
		-5		,			1				5					
act	ggc	cca	acc	ctg	ctg	ctg	ctt	ctg	gtc	agc	ttc	ctc	acc	ttt	gac	295
Thr	Gly	Pro	Ala	Leu	Leu	Leu	Leu	Leu	Val	Ser	Phe	Leu	Thr	Phe	Asp	
10					15					20					25	
ctg	ctc	cat	agg	ccc	gca	ggt	cac	act	ctg	cca	cag	cgc	aaa	ctt	ctc	343
Leu	Leu	His	Arg	Pro	Ala	Gly	His	Thr	Leu	Pro	Gln	Arg	Lys	Leu	Leu	
				30					35					40		
acc	aġg	ggc	cag	agt	cag	aaa	gcc	ggt	gaa	ggt	cct	gga	cag	cag	gag	391
Thr	Arg	GIŢ	Gin	Ser	Gln	Gly	Ala	Gly	Glu	Gly	Pro	Gly	Gln	Gln	Glu	
			45					50					55			
gct	cta	ctc	ctg	caa	atg	ggt	aca	gtc	tca	gga	caa	ctt	agc	ctc	cag	439
Ala	Leu	Leu	Leu	Gln	Met	Gly	Thr	Val	Ser	Gly	Gln	Leu	Ser	Leu	Gln	
		60					65					70				
gac	gca	ctg	ctg	ctg	ctg	ctc	atg	999	ctg	ggc	ccg	ctc	ctg	aga	gcc	487
Asp	Ala	Leu	Leu	Leu	Leu	Leu	Met	Gly	Leu	Gly	Pro	Leu	Leu	Arg	Ala	
<b>.</b>	75					80					85					
tgt	ggc	atg	CCC	ttg	acc	ctg	ctt	ggc	ctg	gct	ttc	tgc	ctc	cat	cct	535
Cys	Gly	Met	Pro	Leu	Thr	Leu	Leu	Gly	Leu	Ala	Phe	Cys	Leu	His	Pro	
90					95					100					105	
tgg	gcc	tgag	agcc	cc t	cccc	acaa	c to	agtg	tcct	tca	aata	tac	aatg	jacca	CC	591
Trp	Ala															
CTTC	ttca	aa a	aaa								i					605

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<222> 46..150

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		acc Thr														105
		ctg Leu														153
		tca Ser														201
		ata Ile 20														249
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<222> 397..402

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		g cag t Gln													147
		c cac e His 25													195
		t tca s Ser													240



	•									
tgagtgggag agtgggctgg gatgtgcatc ctgctccctg aaccettcca tccgagactg tgcccacatc cgaagcacaa ggacatcaaa tcatcagcac aagaacatca acaggaatgccaccetcccc agtgtctgaa ctccctgtcc ctgtcaaatg aaccagaaca aatgcccatgaaaaaaaaaa	300 360 420 432									
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Met Leu Gly Ala Glu Thr Glu Glu 1 5	112									
aag ctg ttt gat gcc ccc ttg tcc atc agc aag aga gag cag ctg gaa Lys Leu Phe Asp Ala Pro Leu Ser Ile Ser Lys Arg Glu Gln Leu Glu 10 15 20	160									
cag cag gtc cca gag aac tac ttc tat gtg cca gac ctg ggc cag gtg Gln Gln Val Pro Glu Asn Tyr Phe Tyr Val Pro Asp Leu Gly Gln Val 25 30 35 40	208									
cct gag att gat gtt cca tcc tac ctg cct gac ctg ccc ggc att gcc Pro Glu Ile Asp Val Pro Ser Tyr Leu Pro Asp Leu Pro Gly Ile Ala 45 50 55	256									
aac gac ctc atg tac att gcc gac ctg ggc ccc ggc att gcc ccc tct Asn Asp Leu Met Tyr Ile Ala Asp Leu Gly Pro Gly Ile Ala Pro Ser 60 65 70	304									
gcc cct ggc acc att cca gaa ctg ccc acc ttc cac act gag gta gcc Ala Pro Gly Thr Ile Pro Glu Leu Pro Thr Phe His Thr Glu Val Ala 75 80 85	352									
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seq TFCLIFGLGAVWG/LG

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ttg atc ttc ggt ctc gga gca gtt tgg ggg ctt ggt gtg gac cct tcc 160
Leu Ile Phe Gly Leu Gly Ala Val Trp Gly Leu Gly Val Asp Pro Ser
-10 -5 1 5

cta cag att gac gtc tta aca gag tta gaa ctt ggg gag tcc acg acc 208 Leu Gln Ile Asp Val Leu Thr Glu Leu Glu Leu Gly Glu Ser Thr Thr 10 15 20

gga gtg cgt cag gtc ccg ggg ctg cat aat ggg acg aaa gcc ttt ctc 256
Gly Val Arg Gln Val Pro Gly Leu His Asn Gly Thr Lys Ala Phe Leu
25 30 35

ttt caa gat act ccc aga agc ata aaa gca tcc act gct aca gct gaa 304
Phe Gln Asp Thr Pro Arg Ser Ile Lys Ala Ser Thr Ala Thr Ala Glu
40 45 50

cag ttt ttt cag aag ctg aga aat aaa cat gaa ttt act att ttg gtg 352
Gln Phe Phe Gln Lys Leu Arg Asn Lys His Glu Phe Thr Ile Leu Val
55 60 65 70

acc cta aaa cag acc cac tta aat tca gga gtt att ctc tca att cac

Thr Leu Lys Gln Thr His Leu Asn Ser Gly Val Ile Leu Ser Ile His

75

80

85

cac ttg gat cac agg taaatgtggt tgctggagtt tcctgtgttt tcattatatg 455 His Leu Asp His Arg

tggttaaatg aatatattaa agagaagtaa acaaaaaaaa aaaaaa 501

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Met Cys Cys Tyr Cys Arg Ile

-40

ttt tgt ctt aga tgt acg tac ttt cct gtt cat tgt ggt atg tgt aat
Phe Cys Leu Arg Cys Thr Tyr Phe Pro Val His Cys Gly Met Cys Asn
-35

-30

-25

ttg cgt tac ttt gaa ttt tcc acg ttt tta ctt tct ttg tct ctc atc
Leu Arg Tyr Phe Glu Phe Ser Thr Phe Leu Leu Ser Leu Ser Leu Ile

-15



Thr	Tyr	Cys	Phe	Trp	Asp 1	Pro	Pro	His	Arg 5	Gly	Ser	His	Ser	ctc Leu 10	tcc Ser	316	5
Leu	gag Glu	His	Thr 15	Pro	Leu	Asp	Phe	Leu 20	Glu	Trp	Gly	Leu	Leu 25	Arg		361	1
tgaa gttt	egett	tc o	gcac	ttat	g to	gcaga latat	ttat	ttt ccc	caga :	ggg	tata	ataga	aat t	cago	gcagct	42] 454	_

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ccaacaccag gaagagtctg aagagcagcc agtgtttcgg cttgtgccct gtata agctgccaaa caagtacggt agttctgaaa atccagaatg gcttgatgtt tac a cac att tta caa ctg ctt act aca gtg gat gat gga att caa gca His Ile Leu Gln Leu Leu Thr Thr Val Asp Asp Gly Ile Gln Ala -40 -35 -30	atg 116 Met att 164 Ile
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<u>.</u>	105		· Val	Ala	GIII	110	val	пуѕ	GIU	СТУ		ьeu	ser	гÀг	Gin		
22			. + < +	~~~							115						
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12°	s cys	, ser	Ser	Ala			Asn	Leu	. ьеи			Tyr	Ser	Pro			
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٧a.	I GIC	ASP	Phe			тте	Leu	Arg			Asp	Lys	Ala				
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_		_	- 33 - 2	,-55	Met	Gln	Val	Δla	Leu	Lve	Glu	Aen	T.eu	Acn	900 Ala	231	
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Leu	Lys	Ğlu	Lys	Phe	Ara	Thr	Met	Glu	Ser	Aen	Gln	Lac	Ser	Ser	Phe	213	
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Gln	Glu	Ile	Pro	Lvs	Len	Acn	Glu	Glu	T.O.	LOU	age Sor	Tura	Cla	Tura	Caa	327	
		30		Ly 3	пец	ASII	35	GIU	пеu	пеа	ser		GIII	гàг	GIII		
ctt	gag		a++	<b>~</b> ~ ~	+ = +	~~~		-+-				40					
Len	Glu	Lve	att	Glu	502	99a	gag	Mos	991	ttg	aac	aaa	gtc	rgg	ata	375	
200	45	Lys	Ile	GIU	SET		GIU	Mec	GIY	Leu		гàг	vaı	Trp	TIE		
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60	116	TIII	Glu	MEL		ьys	GIN	тте	ser		Leu	Thr	Ser	Ala			
	<b>65</b> -	<b>-</b> -			65	, ,				70					75		
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act tta aac agc gtc cat ctt gct gtg gaa gca cta cag aaa act gtg

Thr Leu Asn Ser Val His Leu Ala Val Glu Ala Leu Gln Lys Thr Val

gat gaa cac aag aaa acg atg gaa tta ctg cag agt gat atg aat cag

115

110

Met Pro His Ser Ser Leu



Asp	Glu 125	His	Lys	Lys	Thr	Met 130	Glu	Leu	Leu	Gln	Ser 135	Asp	Met	Asn	Gln	
		_	_	gag Glu				_		_			_			663
	_			gaa Glu 160		_					_	_		_		711
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Ile Tyr Phe Tyr Tyr Ser Leu Pro Asn Ala Val Gly Pro Pro Phe Thr

tcatcatcca gagcagccag tgtccgggag gcagaag atg ccc cac tcc agc ctg

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taa	ato	ctt	acc	70	a+~	~~~		+	75					80		
Trp	Met	Leu	Ala 85	Leu	Leu	Gly	Leu	Ser 90	Gln	Ala	Leu	Asn	Ile	Leu	ctg Leu	439
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130	ьeu	Arg	-ren	тте	ьеи 135	Pro	GIU	Leu	GIn	Ala 140	Arg	Ile	Arg	Thr	Tyr 145	
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Tyr	Ile	Leu	Leu 165	Pro	Leu	Asp	Cys	Gly 170	Val	Pro	Asp	Asn	Leu 175	Ser	Met	
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nsp	195	Ata	GIY	116	гàг	200	Arg	vaı	ıyr	ser	Asn 205	Ser	Ile	Tyr	Glu	
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290 ata	aac	200	++-		295					300					305	
gtg Val	Gly	Ser	Leu	aag Lys 310	Thr	Ser	Ala	gtg Val	Pro 315	agt Ser	acc Thr	tcc Ser	Thr	Met	tcc Ser	1111
caa	qaq	cct			ctc	ata	agt	aaa		aas	227	CCC	ctc	320	ata	1159
Gln	Glu	Pro	Glu 325	Leu	Leu	Leu	Ser	Gly 330	Met	Gly	Lys	Pro	Leu 335	Pro	Leu	1139
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			cag					ctg					cca	tcc Ser		244
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gac Asp 90	gca	agc Ser	tct Ser	gcc Ala	ttt Phe 95	tcc	cca Pro	gcc Ala	tcc Ser	cct Pro 100	gca	aca Thr	cca Pro	aat Asn	gga Gly 105	340
acc	_				aaa Lys					100					100	361
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agc	tcc			tct	cct					gga					cga Arg	95

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40

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Leu Ile Pro Ser Met Leu Ser Arg Ala Ala Gly Trp Cys Trp Tyr Lys
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Glu Pro Thr Gln Gln Phe Ser Tyr Leu Cys Leu Pro Cys Leu Ser Trp
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tgccaggage teetteete tagcaattte tactaaaatg tecaagtaga atgttteett
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	_		site 1150													
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															ccagg	180
												agc				228
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Phe	Tyr	Arg	Arg	Met	Gln	Asn	Ser	Asp	Phe	Leu	Arg	Glu	Leu	Val		
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		_		_								Leu			Glu	
190					195					200					205	
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val	Asp	Leu	Pro	Lys 210	ьeu	Asp	GIÀ	Ala	Leu 215	GIÀ	ьeu	Ser	ьеи	G1u 220	TIE	
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					-30					-25				Thr	-20		
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	Phe	Gly	Asp 1	Pro	Ala	Tyr	Leu 5	Gln	Leu	Ala	His	Gly 10	Tyr	Val	Lys	Gln	
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	Ser	Leu	Asn	Cys	Leu	Thr	Lys	Arg	Ser	Ile	Thr	Phe	Leu	Cys	Gly	Asp	
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	Ile	Asp	Pro	His	Ala	Pro	Asn	Glu	Met	Leu	Tyr	Gly	Arg	Ile	Gly	Tyr	
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	Pro	Gln	Ser	His	Ile	Gln	Gln	Ile	Cys	Glu	Thr	Ile	Leu	Thr	Ser	Gly	
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	gaa	aac	cta	gct	agg	aag	aga	aac	ttc	acg	gca	aag	tct	cca	ctg	atg	537
	GIU	Asn	Leu	Ala	Arg	Lys	Arg	Asn	Phe	Thr	Ala	Lys	Ser	Pro	Leu	Met	
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Tyr	Glu	Trp	_	Gln	Glu	Tyr	Tyr		Gly	Ala	Ala	His		Leu	Ala	
			130					135					140		•	
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Gly	Ile	Tyr	Tyr	Tyr	Leu	Met	Gln	Pro	Ser	Leu	Gln	Val	Ser	Gln	Gly	
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aag	tta	cat	agt	ttg	gtc	aag	CCC	agt	gta	gac	tac	gtc	tgc	cag	ctg	681
Lys	Leu	His	Ser	Leu	Val	Lys	Pro	Ser	Val	Asp	Tyr	Val	Cys	Gln	Leu	
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175				-	180	-			-	185	•	•		_	190	
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atc	cad	acc	tat		gta	ttc	aga	aaa		220	tat	ctc	tat		acc	825
					Val											
110	0111	ALG	210	Ly 3	· uı	2110	A. 9	215	Oru	Ly S	- 7 -	שכע	220	طرحت	n.a	
+		+~+		~~+	~+~	2+4	+~~		+ - +	~~~	ندحه	a+ a		224	~~~	873
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					ggt											921
Tyr		Leu	Cys	His	Gly		Ala	GIÀ	Asn	Ala		Ala	Pne	Leu	Thr	
	240					245					250					
					cag											969
	Tyr	Asn	Leu	Thr	Gln	Asp	Met	Lys	Tyr		Tyr	Arg	Ala	Cys		
255					260					265					270	
					tta											1017
Phe	Ala	Glu	Trp	Cys	Leu	Glu	Tyr	Gly	Glu	His	Gly	Cys	Arg	Thr	Pro	
				275					280					285		
gac	acc	cct	ttc	tct	ctc	ttt	gaa	gga	atg	gct	999	aca	ata	tat	ttc	1065
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					Val											
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Leu		- 55		<i>,</i>	<b>,</b>		,		5	J			5			
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			_		-	_	-		_	_			-		atcatt	1286
			_			-									cctaaa	1346
			_	_											cttgga	1406
		_	_	_				_	-					_		1466
				_	_	_			_		_		add i	acyc	taaaa	
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attttggtca aggaatgata	tctttaga catagaaa	ag ttatcagg ag attttatt cc aagtta a	aa tgtgtttaaa tt aaaatgagtt tg caa atg ga	ctctgtagat atto acaagaagag aact gtaaagcttg tgtt c aca ttt ttt at	tttcta 240 tctttg 300 g tca 353
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cttataagaa ttttaagaac taaaaaaaaa aaaa	554

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Ser Ala Glu Asp Glu Lys Arg Lys Arg Lys Cys Gln Lys His Ala Pro

110

105



														ccc		541
	Asn	Ser	Ala	Gln		Leu	Asp	Asn	Val	_	Gln	Thr	Gly	Pro		
120	<b>+</b> = =				125					130					135	500
														cct Pro		589
11.20		<i></i> , <i></i>	O <sub>1</sub>	140			71011	nop.	145	110	Ly S	01	001	150	017	
tcc	act	tcc	cct		ccc	cct	cat	aca		agc	cgc	aag	cag	tgg	cgg	637
														Trp		
			155					160					165			
		_	_		_	_	_	_	_		_		_	cca		685
Asn	Arg	170	ьys	Asn	гуs	Arg	Arg	Cys	гàг	Asn	гÀг	Pne 180	Gin	Pro	Pro	•
cag	ata		gac	cag	acc	cca		gag	acc	CCC	aca		aaq	aca	gag	733
							-							Thr	_	. 33
	185		•			190					195		•			
														<b>9</b> 99		781
	Ser	Pro	Val	Pro	_	Thr	Asp	Ser	His	_	Ala	Arg	Ala	Gly		
200					205					210					215	202
														cgc Arg		829
Deu	Arg	ALG	AT 9	220	VIG	GIII	Arg	пец	225	GIY	MIG	Arg	FIIC	230	ıyı	
ctc	aat	gaa	cag		tac	tca	ggg	ccc		agt	act	qca	caq	cgt	ctc	877
														Arg		
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Phe	Gln		Asp	Pro	Glu	Ala		Leu	Leu	Tyr	His	_	Gly	Phe	Gln	
200	C22	250	224	224	+~~	<b>CC3</b>	255	<b>636</b>		~+~	~~~	260	2+0	gcc	200	973
														Ala		9/3
	265		_, _	2,5		270		· · · · ·		• • • •	275	<b></b> 9	110	77.4	J	
gat	ctt	cgc	cag	cgg	cct	gca	tcc	cta	gtg	gtg	gct	gac	ttc	ggc	tgt	1021
Asp	Leu	Arg	Gln	Arg	Pro	Ala	Ser	Leu	Val	Val	Ala	Asp	Phe	Gly	Cys	
280					285					290					295	
														tgc		1069
GIY	Asp	Cys	Arg	300	Ата	Ser	Ser	TIE	305	Asn	Pro	vaı	HIS	Cys 310	Pne	
gac	tta	act	tct		gac	cct	agg	atc		ata	tat	gac	ato	gcc	caq	1117
														Ala		
			315		_		_	320			-	_	325			
														ctt		1165
Val	Pro		Glu	Asp	Glu	Ser		Asp	Val	Ala	Val		Cys	Leu	Ser	
cta	ato	330	200	220	atc	200	335	++~	cta	<b>~</b> ~ ~	<b>~~~</b>	340	22 <b>+</b>	aga	at a	1213
														Arg		1213
	345	1				350	<u>-</u>				355			5		
ctg	aag	cca	999	ggt	ctc	ctg	aaa	gtg	gct	gag	gtc	agc	agc	cgc	ttt	1261
	Lys	Pro	Gly	Gly	Leu	Leu	Lys	Val	Ala	Glu	Val	Ser	Ser	Arg	Phe	
360					365					370					375	
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Giu	MSD	vaı	Arg	380	Pne	ьeu	Arg	Ala	385	Thr	гÀг	Leu	GIY	Phe 390	гÀг	
att	atc	tcc	aaa		cta	acc	aac	agc	•	ttc	ttc	tta	ttt	gat	ttc	1357
														Asp		
			395	_				400					405	_		
														tca		1405
Gln	Lys		Gly	Pro	Pro	Leu		Gly	Pro	Lys	Ala		Leu	Ser	Gly	
C+~	C = ~	410	~ ·	<b>~~</b>	+~+	c+-	415	a ~ ~		a	+~	420	- ~~	. + ~ + 4		1450
Leu	Gln	Len	Gln	Pro	Cve	Leu	Tvr	Lvc	Ara	499 Arc	Lya		-99 8	acctl	ccttg	1458
	425		O 1 11	110	Cy B	430	~ <u>Y</u> ~	-73	A. y	nr 9						
agag		agg d	cagat	toto	aa a	-	aggct	cag	gaact	gtg	aaga	actgi	ttt (	ccgg	cctggc	1518
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<210> 109

<211> 714

<212> DNA

<213> Homo sapiens

atcgttacag gcaggtttca ctcaaaaaaa aaaaac

<220>

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<222> 84..332



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gct g Ala A			_			_					_		_		161
gcg c															209
ccg ac Pro Ti	hr Pro														257
	at ggg sn Gly														305
	gc gtt er Val		_	_		_	_	tgaa	aaggo	cac t	tga	ggga	cc		352
ttagc	agcat	cctca	acag	g co	ttgt	aggg	g aat	gee	agaa	gaag	cagi	tcc	ttgg	ccgggc	412
_	_		_	-	_			-	_		-			acctga	
				_										aaatac	
														gaggca	
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<222> 32..718

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<221> polyA\_site <222> 793..805

<400> 110

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Gly 1	Ala	Ala	Gly	Phe 5	Thr	Pro	Ser	Leu	Asp 10	Ser	Asp	Phe	Thr	ttt Phe 15	Thr	148
ctt Leu	Pro	gcc Ala	ggc Gly 20	cag Gln	aag Lys	gag Glu	tgc Cys	ttc Phe 25	tac Tyr	cag Gln	ccc Pro	atg Met	ccc Pro	ctg Leu	aag Lys	196
gcc	tcg	ctg		atc	gag	tac	caa		tta	qat	qqa	qca		tta	gat	244
Ala	Ser	Leu 35	Glu	Ile	Glu	Tyr	Gln 40	Val	Leu	Asp	Gly	Ala 45	Gly	Leu	Asp	
att	gat	ttc	cat	ctt	gcc	tct	cca	gaa	ggc	aaa	acc	tta	gtt	ttt	gaa	292
	50					55					60			Phe		
caa Gln	aga	aaa	tca	gat	gga	gtt	cac	act	gta	gag	act	gaa	gtt	ggt	gat	340
65	nr 9	Бys	SEI	Asp	70	val	nis	1111	vaı	75	Inr	GIU	vaı	Gly	Asp 80	
tac	atg	ttc	tgc	ttt	gac	aat	aca	ttc	agc	acc	att	tct	gag	aag	gtg	388
Tyr	Met	Phe	Cys	Phe 85	Asp	Asn	Thr	Phe	Ser 90	Thr	Ile	Ser	Glu	Lys 95	Val	
att	ttc	ttt	gaa	tta	atc	ctg	gat	aat	atg	gga	gaa	cag	gca	caa	gaa	436
			100					105					110	Gln		
caa	gaa	gat	tgg	aag	aaa	tat	att	act	ggc	aca	gat	ata	ttg	gat	atg	484
		115					120					125		Āsp		
aaa	ctg	gaa	gac	atc	ctg	gaa	tcc	atc	agc	agc	atc	aag	tcc	aga	cta	532
	130					135					140			Arg		
agc	Lac	agt	999	cac	ata	caa	att	ctg	ctt	aga	gca	ttt	gaa	gct Ala	cgt	580
145	шуз	261	Giy	nis	150	GIII	TIE	neu	Tea	155	Ala	Pne	GIU	Ala	Arg 160	
gat	cga	aac	ata	caa		agc	aac	ttt	gat		atc	aat	ttc	tgg		628
Asp	Arg	Asn	Ile	Gln 165	Glu	Ser	Asn	Phe	Asp 170	Arg	Val	Asn	Phe	Trp 175	Ser	
atg	gtt	aat	tta	gtg	gtc	atg	gtg	gtg	gtg	tca	gcc	att	caa	gtt	tat	676
Met	Val	Asn	Leu 180	Val	Val	Met	Val	Val 185	Val	Ser	Ala	Ile	Gln 190	Val	Tyr	
atg	ctg	aag	agt	ctg	ttt	gaa	gat	aag	agg	aaa	agt	aga	act			718
	Leu	195					200					205				
taaa	acto	ca a	acta	gagt	a co	taac	attg	aaa	aatg	agg	cata	aaaa	tg d	aata	aactg	778
ttac	cagto	aa g	acca	aaaa	la aa	laaaa	a									805

<210> 111

<211> 787

<212> DNA <213> Homo sapiens

<220>

<221> CDS

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<221> sig\_peptide <222> 26..88

<223> Von Heijne matrix



# score 4.4 seq AVASSFFCASLFS/AV

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<221> polyA\_site <222> 775..787

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gtg gct tcc agt ttc ttt tgt Val Ala Ser Ser Phe Phe Cys -10			100
ata gaa gag gga cat att ggg Ile Glu Glu Gly His Ile Gly 5 10			148
act tcg acc agc ggc cct ggt Thr Ser Thr Ser Gly Pro Gly 25			196
tca tat aag tct gtg cag acc Ser Tyr Lys Ser Val Gln Thr 40			244
gta cct tgt ggg act agt ggt Val Pro Cys Gly Thr Ser Gly 55			292
gaa gtg gtg aac ttc ctg gtc Glu Val Val Asn Phe Leu Val 70 75			340
aac tat act gct gac tat gac Asn Tyr Thr Ala Asp Tyr Asp 85 90	<b>5 5</b>		388
cac gaa ctg aac cag ttc tgc His Glu Leu Asn Gln Phe Cys 105			436
att gag ctg ttt gga ctg gaa Ile Glu Leu Phe Gly Leu Glu 120	•		481
taaaagggac cctgagcaag aacatt	ttttc atagcagaca	ggaggactca tccacatcgc	541
cagcaatcat aattaagcaa accgc	ctttt gcaccattta	agatttagga aatcatccaa	601
attactttta atgtttctgc agtaga	_	<del>-</del>	661
tcttttatct gttttggatt cactg			721
tttttctttt taacctcaaa ctaata	agaat tttataaaat	attaattttc tccaaaaaaa	781
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<210> 112

<211> 569

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

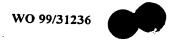
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<221> sig\_peptide

<222> 26..187

<223> Von Heijne matrix

score 4.1





## seq AVVAAAARTGSEA/RV

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gga Gly	acg Thr	gtc Val	gca Ala	Ala	atg Met	gct Ala	gcg Ala	acc Thr	Pro	tca Ser	gca Ala	agg Arg	gct Ala	Ala	gcc Ala		148
				-25					-20					-15			
Ala	Val	gtt Val	Ala -10	Ala	Ala	Ala	Arg	Thr -5	Gly	Ser	Glu	Ala	Arg 1	Val	Ser		196
Lys	Ala 5	gct Ala	Leu	Ala	Thr	Lys 10	Leu	Leu	Ser	Leu	Ser 15	Gly	Val	Phe	Ala		244
Val 20	His	aag Lys	Pro	Lys	Gly 25	Pro	Thr	Ser	Ala	Glu 30	Leu	Leu	Asn	Arg	Leu 35		292
Lys	Glu	aag Lys	Leu	Leu 40	Ala	Glu	Ala	Gly	Met 45	Pro	Ser	Pro	Glu	Trp	Thr	•	340
Lys	Arg	aaa Lys	Lys 55	Gln	Thr	Leu	Lys	Ile 60	Gly	His	Gly	Gly	Thr 65	Leu	Asp	;	388
Ser	Ala	gcc Ala 70	Arg	Gly	Val	Leu	Val 75	Val	Gly	Ile	Gly	Ser 80	Gly	Thr	Lys	•	436
Met	Leu 85	acc Thr	Ser	Met	Leu	Ser	Gly	Ser	Lys	Arg	Tyr 95	Thr	Ala	Ile	Gly	4	484
Glu 100	Leu	Gly aaa	Lys	Ala	Thr 105	Asp	Thr	Leu	Asp	Ser 110	Thr	gly ggg	aag Lys	gta Val	aca Thr 115		532
gaa Glu	gaa Glu	aaa Lys	Pro	tac Tyr 120	ggt Gly	atg Met	aac Asn	ctc Leu	atc Ile 125	taag	rtag					5	569

<210> 113

<211> 893

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> 4..810

<221> sig\_peptide

<223> Von Heijne matrix score 6.8 seq AVMLYTWRSCSRA/IP

<221> polyA\_signal

<222> 858..863

<221> polyA\_site

<222> 881..893



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			gag					gac Asp								96
								gct Ala								144
								att Ile								192
								atg Met								240
gcg Ala	gtc Val	atg Met	ctg Leu -10	tac Tyr	acc Thr	tgg Trp	cgc Arg	agc Ser -5	tgt Cys	tcc Ser	cgg Arg	gcc Ala	att Ile 1	ccc Pro	cag Gln	288
								cga Arg								336
								acc Thr								384
								ttc Phe								432
								ttt Phe 60								480
			aag					ttt Phe								528
								gac Asp								576
								gat Asp								624
cag Gln	aac Asn	ctt Leu	tcc Ser	atg Met 120	ttc Phe	ctg Leu	gcc Ala	aac Asn	cac His 125	aac Asn	agg Arg	atc Ile	acc Thr	cag Gln 130	tgt Cys	672
								cca Pro 140								72
								tac Tyr								76
		_				_		ctc Leu	_	-						81
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<210> 114

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<213> Homo sapiens

1329

1389



<220> <221> CDS <222> 55..459 <221> sig\_peptide <222> 55..120 <223> Von Heijne matrix score 7.2 seg GLWLALVDGLVRS/SP <221> polyA\_signal <222> 1444..1449 <221> polyA\_site <222> 1462..1475 <400> 114 cagtteegea getacgtgtg ggaccegetg etgateetgt egeagategt eete atg 57 105 Gln Thr Val Tyr Tyr Gly Ser Leu Gly Leu Trp Leu Ala Leu Val Asp -15 -10 ggg cta gtg cga agc agc ccc tcg ctg gac cag atg ttc gac gcc gag 153 Gly Leu Val Arg Ser Ser Pro Ser Leu Asp Gln Met Phe Asp Ala Glu 1 atc ctg ggc ttt tcc acc cct cca ggc cgg ctc tcc atg atg tcc ttc 201 Ile Leu Gly Phe Ser Thr Pro Pro Gly Arg Leu Ser Met Met Ser Phe 15 20 atc ttc aac gcc ctc acc tgt gcc ctg ggc ttg ctg tac ttc atc cgg 249 Ile Phe Asn Ala Leu Thr Cys Ala Leu Gly Leu Leu Tyr Phe Ile Arg 35 cga gga aag cag tgt ctg gat ttc act gtc act gtc cat ttc ttt cac 297 Arg Gly Lys Gln Cys Leu Asp Phe Thr Val Thr Val His Phe Phe His 50 55 ete etg gge tge tgg tte tae age tee egt tte eec teg geg etg ace 345 Leu Leu Gly Cys Trp Phe Tyr Ser Ser Arg Phe Pro Ser Ala Leu Thr 65 70 tgg tgg ctg gtc caa gcc gtg tgc att gca ctc atg gct gtc atc ggg 393 Trp Trp Leu Val Gln Ala Val Cys Ile Ala Leu Met Ala Val Ile Gly 85 gag tac ctg tgc atg cgg acg gag ctc aag gag ata ccc ctc aac tca 441 Glu Tyr Leu Cys Met Arg Thr Glu Leu Lys Glu Ile Pro Leu Asn Ser 95 100 gcc cct aaa tcc aat gtc tagaatcagg ccctttggac atcccgctga 489 Ala Pro Lys Ser Asn Val 110 cacttgggcc ccttaacacc ttgggctgct cagaccctcc agatgaggtc cagcccagat 549 ctgagaggaa ccctggaaat gtgaagtctc tgttggtgtg ggagagatag tgagggcctg 609 tcaaagaagg caggtagcag tcagcatgac agctgcaaga atgacctctg tctgttgaag 669 ccttggtatc tgagaggtca ggaaggggac ctctttgagg gtaataacat aattggaacc 729 atgccactct tgagccacaa tacctgtcac cagcctgttg ttttaagaga gaaaaaaaat 789 caaggatate tgattggage aaaccactte tttagteate tgtettaeet eeetgggaca 849 gctgttacct ttgcagtgtt gccgaatcac agcagttacc tttgcaatgt tgccgaatca 909 cagcagttct gttggagaaa cgcttggttt ccggatccag agccacagaa agaaatgtag 969 gtgtgaagta ttaggctgct gtcagggaga ggatggcaga tggaggcatc aagcacaagg 1029 aaaatgcaca acctgtgccc tgttatacac acgttcatgt gcgcccaaga acctatgact 1089 ttcttccagt tccttctacc aggtccccat cctgctgcca gctctcaaca tagcaggcca 1149 taggacccag agaagaatcc cagtgttgct caaagtctga ccatcataaa gacactgcct 1209 gtcttctagg aatgaccagg cacccagctc ccactggact ccaattttt ttcctgcctt

atttagaatt ctttggcggg aagggtatga tgggttccca gagacaagaa gcccaacctt

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gtattttcca tgaaaaaaa aaaaaa 1475 <210> 115 <211> 321 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 48..248 <221> sig\_peptide <222> 48..161 <223> Von Heijne matrix score 6.3 seq LVFALVTAVCCLA/DG <221> polyA\_signal <222> 283..288 <221> polyA site <222> 308..321 <400> 115 56 gctgagaaga gttgagggaa agtgctgctg ctgggtctgc agacgcg atg aat aac Met Asn Asn gtg cag ccg aaa ata aaa cat cgc ccc ttc tgc ttc agt gtg aaa ggc 104 Val Gln Pro Lys Ile Lys His Arg Pro Phe Cys Phe Ser Val Lys Gly -30 -25 cac gtg aag atg ctg cgg ctg gtg ttt gca ctt gtg aca gca gta tgc 152 His Val Lys Met Leu Arg Leu Val Phe Ala Leu Val Thr Ala Val Cys -5 -10 -15 200 tgt ctt gcc gac ggg gcc ctt att tac cgg aag ctt ctg ttc aat ccc Cys Leu Ala Asp Gly Ala Leu Ile Tyr Arg Lys Leu Leu Phe Asn Pro 5 aac ggt cct tac cag aaa aag cct gtg cat gaa aaa aaa gaa gtt ttg 248 Asn Gly Pro Tyr Gln Lys Lys Pro Val His Glu Lys Lys Glu Val Leu 20 25 tgattttata ttacttttta gtttgatact aagtattaaa catatttctg tattcttcca 308 321 aaaaaaaaa aaa <210> 116 <211> 450 <212> DNA <213> Homo sapiens

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agg aga cag agg ctg gcc gag ctg cag gcc aaa cac ggg gat cct ggt Arg Arg Gln Arg Leu Ala Glu Leu Gln Ala Lys His Gly Asp Pro Gly -45 -40 -35 -30	99
gat gcg gcc caa cag gaa gca aag cac agg gaa gca gaa atg aga aac Asp Ala Ala Gln Gln Glu Ala Lys His Arg Glu Ala Glu Met Arg Asn -25 -20 -15	147
agt atc tta gcc caa gtt ctg gat cag tcg gcc cgg gcc agg tta agt Ser Ile Leu Ala Gln Val Leu Asp Gln Ser Ala Arg Ala Arg Leu Ser	195
aac tta gca ctt gta aag cct gaa aaa act aaa gca gta gag aat tac Asn Leu Ala Leu Val Lys Pro Glu Lys Thr Lys Ala Val Glu Asn Tyr 5 10 15	243
ctt ata cag atg gca aga tat gga caa cta agt gag aag gta tca gaa Leu Ile Gln Met Ala Arg Tyr Gly Gln Leu Ser Glu Lys Val Ser Glu 20 25 30 35	291
caa ggt tta ata gaa atc ctt aaa aaa gta agc caa caa aca gaa aag Gln Gly Leu Ile Glu Ile Leu Lys Lys Val Ser Gln Gln Thr Glu Lys 40 45 50	339
aca aca aca gtg aaa ttc aac aga aga aaa gta atg gac tct gat gaa Thr Thr Thr Val Lys Phe Asn Arg Arg Lys Val Met Asp Ser Asp Glu 55 60 65	387
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	•				-											
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								aac Asn								531
								gca Ala								579
								gtt Val								627
								gca Ala								675
Leu	Val	Gln	Glu 205	Glu	Phe	Leu	Gln	aga Arg 210	Leu	Asp	Phe	Tyr	Gln 215	His	Ser	723
Trp	Leu	Pro 220	Ala	Arg	Ala	Leu	Val 225	gaa Glu	Glu	Ala	Leu	Ala 230	Gln	Arg	Phe	771
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Pro 250	Trp	Lys	Glu	His	Leu 255	Tyr	His	ctg Leu	Glu	Ser 260	Gly	Leu	Ser	Pro	Pro 265	867
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Ile	Gln	Cys	Val 285	Pro	Lys	Glu	Pro	cac His 290	Ser	Phe	Gln	Ser	Arg 295	Leu	Pro	963
Leu	Pro	Glu 300	Pro	Trp	Arg	Gly	Leu 305		Asp	Glu	Ala	Leu 310	Asp	Gln	Val	1011
Ser	Gly 315	Ile	Pro	Gly	Cys	Ile 320	Phe		His	Ala	Ser 325	Gly	Phe	Ile	Gly	1059
Gly 330	His	Arg	Thr	Arg	Glu 335	Gly	Ala		Ser	Met 340	Ala	Arg	Ala	Thr	Leu 345	1107
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350 355

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				atc Ile													206
7	Thr	Gly	Leu	cag Gln	Ser 20	Leu	Leu	Gln	Gly	Phe 25	Ser	Arg	Leu	Phe	Leu 30	Lys	254
				ctt Leu 35													302
				ctc Leu													350
C	Gln	Leu 65	Gly	aac Asn	Asn	Thr	Leu 70	Ser	Ser	His	Leu	Gln 75	Ile	Asp	Lys	Val	398
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1	Lys	Leu	Pro	Arg 115	Arg	Arg	Ser	His	Gln 120	Asp	Ala	Leu	Glu	Gly 125	Gly		
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agg ccc tct cgg cag ctg taggggtggg gaccggggag cacctgcctg Arg Pro Ser Arg Gln Leu 180	734
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Cys Cys Lys Gly Gly Pro Asp Glu Asp Ala Val Glu Arg Gln Arg Arg -55 -45	
cag aag ttg ctt ctt gca caa ctg cat cac aga aaa agg gtg aag gca	151
Gln Lys Leu Leu Ala Gln Leu His His Arg Lys Arg Val Lys Ala	
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Thr Leu Val Gln Arg Arg Ile Arg Gln Arg Arg Gln Ala Leu Leu Arg 10 15 20	
gto tac gto ato cag gag cag gcg acg gto aag cto cag too tgc ato	343
Val Tyr Val Ile Gln Glu Gln Ala Thr Val Lys Leu Gln Ser Cys Ile 25 30 35 40	
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Arg Met Trp Gln Cys Arg Gln Cys Tyr Arg Gln Met Cys Asn Ala Leu	
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Cys Leu Phe Gln Val Pro Glu Ser Ser Leu Ala Phe Gln Thr Asp Gly	
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75 80 85	
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Ile Glu Ile Leu Ser Ile 90	
cactacecta ataaatgtet gace	559

443

503

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22t	~=+	+~~	C 2 C	ctc	+c=	acc	tca			C22	ccc	200		caa	ac a	99
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71011	1100		-30	u	501	2124		-25		01	110		-20	<b></b>		
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	_	-15			_		-10					-5				
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Ala	Ser	Ala	Leu	Arg	Ser	Met	Lys	Ser	Ser		Ala	Ala	Arg	Lys	_	
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														gaa		243
Asp	Phe	Leu	Arg		Leu	Ser	Asp	Gly	_	Ser	Gly	Thr	Ser	Glu	His	
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														gct		291
116	Set.	MIG	35	vai	inr	Set	FIO	Arg	TIG	SEL	Cys	uis	45	Ala	AId	
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caaggtatcc tcagaaccat ttggggtgtc ctttggcatt ggataataga aataaaattt 743
tacctctttc tacaaaaaaa aaaaaac 770

Ile Pro Thr Ala Arg Ala Leu Cys Leu Gly Cys Ser Cys Cys Thr Glu
50 55 60

cgc ctc ctc ctg cca ccg ccc tcc ctt tct tta gaa gcc cct gcc Arg Leu Leu Pro Pro Pro Ser Leu Leu Ser Leu Glu Ala Pro Ala

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Met	Ala	Met	Ala	Gln	Lys	Leu	Ser	His	Leu	Leu	Pro	Ser	Leu	Arg	Gln	
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gtc	atc	cag	gag	cct	cag	cta	tct	ctg	cag	cca	gag	cct	gtc	ttc	acg	153
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Val	Asp	Arg	Ala	Glu	Val	Pro	Pro	Leu	Phe	Trp	Lys	Pro	Tyr	Ile	Tyr	
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gcg	ggc	tac	cgg	ccg	ctg	cat	cag	acc	tgg	cgc	ttc	tat	ttc	cgc	acg	249
Ala	Gly	Tyr	Arg	Pro	Leu	His	Gln	Thr	Trp	Arg	Phe	Tyr	Phe	Arg		
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ctg	ttc	cag	cag	cac	aac	gag	gcc	gtg	aat	gtc	tgg	acc	cac	ctg	ctg	297
Leu	Phe	Gln	Gln		Asn	Glu	Ala	Val		Val	Trp	Thr	His		Leu	
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gcg	gcc	ctg	gta	ctg	ctg	ctg	cgg	ctg	gcc	ctc	ttt	gtg	gag	acc	gtg	345
Ala	Ala	Leu		Leu	Leu	Leu	Arg		Ата	ьeu	Pne	vaı		Thr	vaı	
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gac	ttc	tgg	gga	gac	cca	cac	gcc	ctg	CCC	CTC	Dr-	atc	Tlo	gcc	Lou	393
Asp	Pne		GIÀ	Asp	Pro	His		Leu	Pro	Leu	Pne		TTE	vaı	пеп	
		80					85					90		a+a	~ ~ ~	441
gcc	tet	בבכ	acc	tac	CCC	tcc	Tou	agt	315	LLG	71-	Tic	Leu	Leu	Gln	747
Ala		Pne	Thr	Tyr	тел	Ser	ьeu	ser	Ala	ьeu	105	пть	neu	пец	GIII	
	95					100 cat	+ > 0	200	++-	++0		cta	G a C	tat	ata	489
gcc	aag	Cor	gag	Dho	rgg T	His	Three	Sex	Dhe	Dhe	Dhe	Len	Acn	Tyr	Val	
110	пув	Ser	GIU	Pne	115	nis	TAT	261	FIIE	120	FIIC	пец	vob	- y -	125	
	~+~	~~~	ata	+ > 0		ttt	aac	act	acc		aca	cac	ttc	tac		537
333	Val	Ala	Val	Tyr	Gln	Phe	Glv	Ser	Ala	Len	Δla	His	Phe	Tvr	Tvr	
Gry	Val	ATA	VAI	130	GIII	1110		-	135					140	- 2 -	
act	atc	gag	ccc		taa	cat	acc	cag		caq	act	att	ttt	ctq	ccc	585
Ala	Ile	Glu	Pro	Ala	Tro	His	Ala	Gln	Val	Gln	Ala	Val	Phe	Leu	Pro	
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ato	act	acc		ctc	acc	tgg	ctt		tac	att	ggc	tcc	tgc	tat	aac	633
Met	Ala	Ala	Phe	Leu	Ala	Trp	Leu	Ser	Cys	Ile	Gly	Ser	Cys	Tyr	Asn	
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Lys	Tyr	Ile	Gln	Lys	Pro	Gly	Leu	Leu	Gly	Arg	Thr	Cys	Gln	Glu	Val	
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Pro	Ser	Val	Leu	Ala	Tyr	Ala	Leu	Asp	Ile	Ser	Pro	Val	Val	His	Arg	
190					195					200					205	
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Ile	Phe	Val	Ser	Ser	Asp	Pro	Thr	Thr	Asp	Asp	Pro	Ala	Leu			
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His	Lys	Cys	Gln 225	Val	Val	Phe	Phe	Leu 230	Leu	Ala	Ala	Ala	Phe 235	Phe	Ser	
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												tgc Cys				921
Gln 270	Leu	Glu	Ala	Val	Ala 275	Leu	Asp	Tyr	Glu	Ala 280	Arg	cgg Arg	Pro	Ile	Tyr 285	969
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	_	-			_				_			ctg	-	_	_	1065

Leu Thr Val Gly Ser Ser Ile Leu Thr Ala Phe Leu Leu Ser Gln Leu 305 310 315 ∖305 gta cag cgc aaa ctt gat cag aag acc aag tgaaggggga tggcatctgg 1115 Val Gln Arg Lys Leu Asp Gln Lys Thr Lys 320 325

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ggc aca gtg gga ttg tgg aga cgg tgt atc acc ata ccc aaa aac atg	294
Gly Thr Val Gly Leu Trp Arg Arg Cys Ile Thr Ile Pro Lys Asn Met	
55 60 65	
cat tgg tat agc cca cca gaa agg aca gag tca ttt gat gtg gtc aca	342
His Trp Tyr Ser Pro Pro Glu Arg Thr Glu Ser Phe Asp Val Val Thr	
70 75 80	
aaa tgt gtg agt ttc aca cta act gag cag ttc atg gag aaa ttt gtt	390
Lys Cys Val Ser Phe Thr Leu Thr Glu Gln Phe Met Glu Lys Phe Val	
85 90 95 100	420
gat ccc gga aac cac aat agc ggg att gat ctc ctt agg acc tat ctt	438
Asp Pro Gly Asn His Asn Ser Gly Ile Asp Leu Leu Arg Thr Tyr Leu	
105 110 115	406
tgg cgt tgc cag ttc ctt tta cct ttt gtg agt tta ggt ttg atg tgc	486
Trp Arg Cys Gln Phe Leu Leu Pro Phe Val Ser Leu Gly Leu Met Cys	
120 125 130	534
ttt ggg gct ttg atc gga ctt tgt gct tgc att tgc cga agc tta tat	224
Phe Gly Ala Leu Ile Gly Leu Cys Ala Cys Ile Cys Arg Ser Leu Tyr	
133	582
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Pro Thr Ile Ala Thr Gly Ile Leu His Leu Leu Ala Val Thr Lys Glu	
130	630
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165 170 175 180 cac gca tgc gtg caa aca ggg aag ccc aag taggagaaga ggaaagaggt	680
His Ala Cys Val Gln Thr Gly Lys Pro Lys	
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cctcctgata gtagttgaat cctaccttgc atacttaatg catagtgaaa tggcatcta	g 1160
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gcc tcc att ggc aca gac ttc tgg tat gaa tat cga agt cca gtt caa 15 Ala Ser Ile Gly Thr Asp Phe Trp Tyr Glu Tyr Arg Ser Pro Val Gln 5 10 15 20	0													
gaa aat too agt gat ttg aat aaa ago ato tgg gat gaa tto att agt	8													
Glu Asn Ser Ser Asp Leu Asn Lys Ser Ile Trp Asp Glu Phe Ile Ser 25 30 35														
gat gaa gca gat gaa aag act tat aat gat gca cct ttt cga tac aat 24 Asp Glu Ala Asp Glu Lys Thr Tyr Asn Asp Ala Pro Phe Arg Tyr Asn 40 45 50	6													
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cat tgg tat agc cca cca gaa agg aca gag tca ttt gat gtg gtc aca  His Trp Tyr Ser Pro Pro Glu Arg Thr Glu Ser Phe Asp Val Val Thr  70 75 80	2													
aaa tgt gtg agt ttc aca cta act gag cag ttc atg gag aaa ttt gtt 39  Lys Cys Val Ser Phe Thr Leu Thr Glu Gln Phe Met Glu Lys Phe Val  85 90 95 100	0													
gat ccc gga aac cac aat agc ggg att gat ctc ctt agg acc tat ctt 43 Asp Pro Gly Asn His Asn Ser Gly Ile Asp Leu Leu Arg Thr Tyr Leu 105 110 115	8													
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ttt ggg gct ttg atc gga ctt tgt gct tgc att tgc cga agc tta tat 53 Phe Gly Ala Leu Ile Gly Leu Cys Ala Cys Ile Cys Arg Ser Leu Tyr	4													
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						-20					-15					
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-10	Leu	GIĀ	Leu	met	Met -5	val	vai	Thr	GIĀ		Glu	Asp	Glu	Asn	Ser	
	+~+	acc	cat	~~~	_	a+ a	a+ ~			1		_4_		5		
Pro	Cve	Ala	Wie	Glu	312	Leu	Lev	gac	gag	gac	acc	CCC	בכנ	tgc Cys	cag	146
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vaı	Met	vaı	Asp		Asp	Ala	Pro	Ser		Ala	Glu	Pro	Arg	Gln	Arg	
++0	+~~			75					80					85		
Dhe	777	aya	Tic	T~~	ctg	gra	aca	gat	atc	aag	ggc	gcc	gac	ctg	aag	386
1110	ııp	Arg	90	тър	пец	vai	1111	ASP 95	TTE	гÀг	GIY	Ата		Leu	гλε	
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Lys	Gly	Lvs	Ile	Gln	Glv	Gln	Glu	Leu	Ser	Δla	Tur	Cay	Ala	Pro	Ser	434
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GIY	ser	Trp	rys		Asp	Arg	Phe	Leu		Arg	Phe	His	Leu	Gly	Glu	
cct	<b>T</b> 2 2	~~~	200	155					160					165		
Pro	Glu	Δla	Ser	Thr	Cag	Dhe	Mot	Th~	cag	aac	tac	cag	gac	tca Ser	CCa	626
	u	71.24	170	1111	GIII	FIIC	Mec	175	GIII	ASII	Tyr	GIN	180	ser	Pro	
acc	ctc	caq		ccc	aga	gaa	agg		age	a a a	ccc	220		aaa	220	674
Thr	Leu	Gln	Ala	Pro	Ara	Glu	Ara	Ala	Ser	Glu	Pro	Lvs	Hic	Lys	aac	6/4
		185			3		190					195		Ly S	non.	
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Gln	Ala	Glu	Ile	Ala	Ála	Cys	_	_			J		2234			
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ctg ccg gat gag gcc cgg agc ctg ccc ccg ccc aag ctg acc gac ccg Leu Pro Asp Glu Ala Arg Ser Leu Pro Pro Pro Lys Leu Thr Asp Pro	157
cgg ctc ctc tac atc ggc ttc ttg ggc tac tgc tcc ggc ctg att gat Arg Leu Leu Tyr Ile Gly Phe Leu Gly Tyr Cys Ser Gly Leu Ile Asp	205
-10 -5 1 aac ctg atc cgg cgg agg ccg atc gcg acg gct ggt ttg cat cgc cag Asn Leu Ile Arg Arg Pro Ile Ala Thr Ala Gly Leu His Arg Gln	253
5 10 15 ctt cta tat att acg gcc ttt ttt ttg ctg gat att atc ttg Leu Leu Tyr Ile Thr Ala Phe Phe Leu Leu Asp Ile Ile Leu	295
20 25 30 taaaacgtga agactacctg tatgctgtga gggaccgtga aatgtttgga tatatgaaat tacatccaga ggattttcct gaagaagata agaaaacata tggtgaaatt tttgaaaaat	355 415
tccatccaat acgttgaagt cttcaaaatg cttgctccag tttcactgat acctgctgtt cctgaatttg atggaacatg tttcttatga cagttgaagc ttatgctaat ctgtatgttg acaccttgta attaaaatac gtaccaaaaa aaaaaa	475 535 571

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tccaagttga acaccttgg gtctttctat gcgaacggat tgaagaaacg caaaaagttt 420
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301

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gtt aaa aag att gca atg cga gaa gtc aag tta cta aag caa ctt agg Val Lys Lys Ile Ala Met Arg Glu Val Lys Leu Leu Lys Gln Leu Arg 45 50 55	616
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Ala Thr Ser Leu Ala Gly Pro Val Leu Ser Thr Leu Ile Ala Pro Thr -10 -5 1 5	103
Pro Met Leu Phe Cys Glu Asp Lys Ser Trp Asp Leu Phe Leu Phe Phe  10  15  20	151
ag tot cac aag aca tgg ggc ato too aca aat tta agt too tgt coa Lys Ser His Lys Thr Trp Gly Ile Ser Thr Asn Leu Ser Ser Cys Pro 25 30 35	199
Phe Gly Asn Leu Phe Leu Cys Val Gln Phe Val Arg Glu Lys Gln Ser 40 45 50	247
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Ala	Cys	Pro	Ala	Leu	Gly	Thr	Lys	Ser	Cys	Ser	Ser	Ser	Cvs	Ala	Asp	
				-20					-15					-10	_	
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Ser	Phe	Val	Ser	Ser	Ser	Ser	Ser	Gln	Pro	Val	Ser	Len	Dhe	Ser	Thr	212
			-5					1				5			1111	
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Ser	Gln	Glu	Gly	Leu	Ser	Ser	Len	Cvs	Ser	Den	Glu	D~a	602	Cox	gaa	360
	10		-			15		<b>C</b>		rsp	20	PIO	ser	set	GIU	
att	atq	act	tct	tee	ttt		tca	tct	+ =+	<b>~</b> 33		+				400
Ile	Met	Thr	Ser	Ser	Dhe	T.em	Ser	Ser	202	gaa cl.	Tla	tti -	aac	act	ggc	408
25				561	30	Deu	561	261	Set		тте	HIS	Asn	Thr	-	
ctt	aca	ata	cta	cat		~~~				35					40	
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<b>D</b> Cu	T 11T	116	Leu	nis	GIY	GIU	гÀг	ser		Val	Leu	Gly	Ser	Gln	Pro	
<b>-+</b> +				45					50					55		
ali Tl-	tta	900	aaa	aaa	aaa	aaa										477
тте	ьеи	АТА	Lys	Lys	Lys	Lys										

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_	50	-	_														
ctgg	gctgo	ctg g	gtg	cactt	a c	cctc	cttg	g ct:	tggt:	tact	tcat	ttta	ıca	agga	agg	ggt	253
agta	aatto	gc d	cact	tctct	t c	tact	tgga	g gci	tatt	taaa	taaa	aatgt	aa	gact	tca	aaa	313
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	tac aa Tyr Ly			_		_	_				_			-	153
_	ttt tt Phe Ph 25	_		~ ~	_		_				_				201
Pro A	aac tt Asn Ph 40														249
	att gc Ile Al			_	_		_		_			_	_	_	297
	gca gc Ala Al														345
	ttg tt Leu Le	-			_		_	_							393
_	atg cc Met Pr 10	o Pro			_	_						_		_	441
Gly A	aga ta Arg Ty 120														489



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Leu Gly Phe Asn Lys Arg Ala Ile Asp Lys Cys Trp Lys Ile Arg His	000
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Phe Pro Asn Glu Phe Ile Val Glu Thr Lys Ile Cys Gln Glu	675
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Met Ser Ala Arg Ile Pro Phe Tyr Lys Asp Thr Ser Gln Ile Arg	
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Leu Gly Ser Thr Ile Ile Pro His Phe Asn Leu Ile Thr Phe Val Lys 20 25 30	
acc ttt ttc caa ata tagtcactct ctgaggtact gatggttagg atctcaacat	271
Thr Phe Phe Gln Ile	
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Met Met Leu Leu Glu Ser Pro Ile Asp Pro Gln Pro Leu Ser Phe Lys  1 10 15	
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Cag gca gaa agg ctg ttt gaa aat caa ctt gtt gga ccg gag tcc ata	313
Gln Ala Glu Arg Leu Phe Glu Asn Gln Leu Val Gly Pro Glu Ser Ile 35 40 45	
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PCT/IB98/02122 -

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65	ьys	ьeu	GIU	Asn	70	GIU	ile	GIu	Thr	11e 75	Ala	Arg	Phe	Gly	Ser		
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Gly	Pro	Cys	Lys	Thr	Arq	Asp	Asp	Glu	Pro	Val	Cvs	Glv	Ara	Pro	Leu		13,
_		-	•	85		•	-		90		-4 -	1	٠ ي	95			
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Gly	Ile	Arg		Gly	Pro	Asn	Gly		Leu	Phe	Val	Ala		Ala	Cys		
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Lvs	Glv	Len	Dhe	gaa Glu	gta Val	aat Aen	Dro	rgg	aaa	cgt	gaa	gtg	aaa	ctg	ctg		553
פעם	Cly	115	FIIC	GIU	Val	ASII	120	пр	гур	Arg	GIU	125	ьys	Leu	ьeu		
ctg	tcc		gag	aca	ccc	att		aga	aaq	aac	atq		ttt	ata	aat	,	601
Leu	Ser	Ser	Glu	Thr	Pro	Ile	Glu	Gly	Lys	Asn	Met	Ser	Phe	Val	Asn		
	130					135					140						
gat	ctt	aca	gtc	tct	cag	gat	ggg	agg	aag	att	tat	ttc	acc	gat	tct	(	649
	Leu	Thr	Val	Ser		Asp	Gly	Arg	Lys		Tyr	Phe	Thr	Asp			
145	300	222	+~~		150					155					160		
Ser	Ser	Lvs	Trn	caa Gln	Ara	Ara	gac Aen	Tur	CEG	TOU	ctg	grg	atg	gag	ggc	(	697
-		ט גָט		165	A. 9	Ar 9	rsp	TYT	170	neu	ъец	vai	Met	175	GIY		
aca	gat	gac	999	cgc	ctg	ctg	gag	tat	gat	act	gtg	acc	agg	gaa	gta	•	745
Thr	Asp	Asp	Gly	Arg	Leu	Leu	Glu	Tyr	Asp	Thr	Val	Thr	Arg	Glu	Val		
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cct	qca		gac	ttt	atc	cta		gca	gaa	aca	acc		acc	agg	ata	\$	341
Pro	Ala	Glu	Asp	Phe	Val	Leu	Val	Ala	Glu	Thr	Thr	Met	Ala	Arq	Ile	`	711
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cga	aga	gtc	tac	gtt	tct	ggc	ctg	atg	aag	ggc	999	gct	gat	ctg	ttt	8	389
	Arg	Val	Tyr	Val		Gly	Leu	Met	Lys		Gly	Ala	Asp	Leu			
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Val	Glu	Agn	Met	cct Pro	gga	Dhe	Dro	gac	aac	atc	cgg	CCC	agc	agc	tct	٤	937
	014			245	Gry	FIIC	FIO	Top	250	116	Arg	PIO	Ser	255	Ser		
999	999	tac	tgg	gtg	ggc	atg	tcg	acc		cgc	cct	aac	cct		ttt	9	985
Gly	Gly	Tyr	Trp	Val	Gly	Met	Ser	Thr	Ile	Arg	Pro	Asn	Pro	Gly	Phe		
			260					265					270				
tcc	atg	ctg	gat	ttc	tta	tct	gag	aga	CCC	tgg	att	aaa	agg	atg	att	10	33
ser	Met	ьеи 275	Asp	Phe	ьeu	ser		Arg	Pro	Trp	Ile		Arg	Met	Ile		
ttt	aac		222	aaa	222	aa	280					285				1.0	053
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                                                                       112
                             Met Phe Ala Pro Ala Val Met Arg Ala
                                     -30
                                                         -25
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 Phe Arg Lys Asn Lys Thr Leu Gly Tyr Gly Val Pro Met Leu Leu
             -20
                                 -15
att gtt gga ggt tct ttt ggt ctt cgt gag ttt tct caa atc cga tat
                                                                      208
 Ile Val Gly Sly Ser Phe Gly Leu Arg Glu Phe Ser Gln Ile Arg Tyr
gat gct gtg aag agt aaa atg gat cct gag ctt gaa aaa aaa ctg aaa
                                                                      256
Asp Ala Val Lys Ser Lys Met Asp Pro Glu Leu Glu Lys Lys Leu Lys
                     15
                                         20
gag aat aaa ata tct tta gag tcg gaa tat gag aaa atc aaa gac tcc
                                                                      304
Glu Asn Lys Ile Ser Leu Glu Ser Glu Tyr Glu Lys Ile Lys Asp Ser
                 30
aag ttt gat gac tgg aag aat att cga gga ccc agg cct tgg gaa gat
                                                                      352
Lys Phe Asp Asp Trp Lys Asn Ile Arg Gly Pro Arg Pro Trp Glu Asp
            45
                                50
cct gac ctc ctc caa gga aga aat cca gaa agc ctt aag act aag aca
                                                                      400
Pro Asp Leu Leu Gln Gly Arg Asn Pro Glu Ser Leu Lys Thr Lys Thr
                             65
act tgactctgct gattcttttt tccnnntttt ttttttttta aataaaaata
                                                                      453
Thr
ctattaactg gacttcctaa tatatacttc tatcaagtgg aaaggaaatt ccaggcccat
                                                                      513
ggaaacttgg atatgggtaa tttgatgaca aataatcttc actaaaggtc atgtacaggt
                                                                      573
ttttatactt cccagctatt ccatctgtgg atgaaagtaa caatgttggc cacgtatatt
                                                                      633
ttacacctcg aaataaaaa tgtgaatact gctccaaaaa aaaaaaccag taccgtgtag
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tctctctcgt ggcttggatt tacactgggc aacgtggttg gaatgtatct ggctcagaac
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                                                                     873
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cagcacttct cttctttgct agaccctgtg ttttttgctt taaagcaagc aaaatggggc
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ser LMCLSLCTAFALS/KP



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ctt atg tgc ctg tcc ctg tgc aca gcc ttt gcc ttg agc aaa ccc aca Leu Met Cys Leu Ser Leu Cys Thr Ala Phe Ala Leu Ser Lys Pro Thr	102 5									
gaa aag aag gac cgt gta cat cat gag cct cag ctc agt gac aag gtt Glu Lys Lys Asp Arg Val His His Glu Pro Gln Leu Ser Asp Lys Val 5 10 15	150									
cac aat gat att tgatagaacc aattgttgta cataaaacag atctgcgcat His Asn Asp Ile 20	202									
atatatatat gtataaaaaa taataaaata atggaagatg aaaaaaaa	254									
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gcc tcc att ggc aca gac ttc tgg tat gaa tat cga agt cca gtt caa Ala Ser Ile Gly Thr Asp Phe Trp Tyr Glu Tyr Arg Ser Pro Val Gln 5 10 15 20	150									
gaa aat too agt gat ttg aat aaa ago ato tgg gat gaa tto att agt	198									
Glu Asn Ser Ser Asp Leu Asn Lys Ser Ile Trp Asp Glu Phe Ile Ser 25 30 35	•									
gat gag gca gat gaa aag act tat aat gat gca ctt ttt cga tac aat Asp Glu Ala Asp Glu Lys Thr Tyr Asn Asp Ala Leu Phe Arg Tyr Asn 40	246									
ggc aca gtg gga ttg tgg gga cgg tgt atc acc ata ccc aaa aac atg Gly Thr Val Gly Leu Trp Gly Arg Cys Ile Thr Ile Pro Lys Asn Met 55 60 65	294									
cat tgg tat agc cca cca gaa agg aca ggt att tct ctt att tta act His Trp Tyr Ser Pro Pro Glu Arg Thr Gly Ile Ser Leu Ile Leu Thr	342									



70	75	80	
tot gto tto tto acc tgg	tta ata ata gac aaa	acg acg taatgattgc	391
Ser Val Phe Phe Thr Trp	Leu Ile Ile Asp Lys	Thr Thr	•
85 90	95		
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ttggttggat gaggaacttt to	ttatcttg ggaaagcctt	aatggctttt ttttttctta	571
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aaaagtgcat cgaaagactt tt	aaaaatat ttggtaacta	gtaaaaggac taccatcgaa	691
aatcaactca aaaaattgtc ct	tttatggg ttagctgtat	tataatacat atctatcatt	751
tgcccctgtg tcttagagga ta	taatttga ccagctctac	atttaatctg tgtaattatg	811
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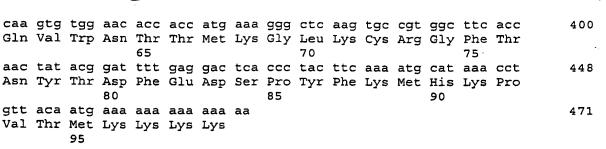
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agt cta aag aag aga cac ttt ttt caa aac tta gga tct att tta acg Ser Leu Lys Lys Arg His Phe Phe Gln Asn Leu Gly Ser Ile Leu Thr 115 120 125	537								
tat gcc ttc ttg gga act gcc atc tcc tgc atc gtc ata ggg Tyr Ala Phe Leu Gly Thr Ala Ile Ser Cys Ile Val Ile Gly 130 135 140	579								
taagtgacat teggagetea agttgeaggt ggetgtgggg tetgtgatet gtgtgagga tetaacactt eagtatet tgetggetgg gaaaattgte ttttttag tatateacat atttgtatgt tttttetgae ttaatteeae ggettetgae aaatacaagg etteaaatea aggaateaet ggaettete tgtgagtet ggaettetga ettagggaat gtggateaet tgeettgagt tatgtgaage geattgeatt	639 699 759 819 879 939 9059 1059 1119 1239 1244								
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tac ttc ctc atc gca gcc ggc gtt gtg gtc ctt gct ctt ggt ttc ctg Tyr Phe Leu Ile Ala Ala Gly Val Val Leu Ala Leu Gly Phe Leu -20 -15 -10 -5	160								
ggc tgc tat ggt gct aag act gag agc atg tgt gcc ctc gtg acg ttc Gly Cys Tyr Gly Ala Lys Thr Glu Ser Met Cys Ala Leu Val Thr Phe 1 5 10	208								
ttc ttc atc ctc ctc ctc atc ttc att gct gag gtt gca gct gct gtg Phe Phe Ile Leu Leu Leu Ile Phe Ile Ala Glu Val Ala Ala Ala Val 15 20 25	256								
gtc gcc ctg gtg tac acc aca atg gct gag cac ttc ctg acg ttg ctg Val Ala Leu Val Tyr Thr Thr Met Ala Glu His Phe Leu Thr Leu Leu 30 35 40	304								
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tat cag etc tat tee ttg etg egg teg gag aag tgg aac cae aca ett

Tyr Gln Leu Tyr Ser Leu Leu Arg Ser Glu Lys Trp Asn His Thr Leu



		PCT/IB9
	•	
		20
4		

5					10					15					20	
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Ser	Met	Ala	Leu	Ile 25	Leu	Phe	Cys	Asn	Tyr 30	Tyr	Val	Leu	Phe	Lys 35	Leu	
ctc	cgg	gac	a.ga	ata	gta	tta	ggc	agg	gca	tac	tcc	tac	cca	ctc	aac	654
Leu	Arg	Asp	Arg	Ile	Val	Leu	Gly	Arg	Ala	Tyr	Ser	Tyr	Pro	Leu	Asn	
			40					45					50			
agt	tat	gaa	ctc	aag	gca	aac	taag	gctgo	cct c	ctcaa	acaat	gag	ggag	gaact	:	705
Ser	Tyr	Glu	Leu	Lys	Ala	Asn										
		55														
caga	taaa	aaa t	tattt	tcat	a co	gttct	attt	: ttt	tctt	gtg	attt	ttat	aa a	atatt	taaga	765
tgtt	ttat	at t	ttgt	atac	t at	tate	gtttt	gaa	agto	ggg	aaga	gtaa	agg g	gatat	taaat	825
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Thr Ala Ala Leu Pro Ala

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                                        -15
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                - 5
Ser Pro Val Phe Gln Ile Pro Lys Asn Asp Asp Ile Pro Glu Gln Asp
       10
                            15
Ser Leu Gly Leu Ser Asn Leu Gln Lys Ser Gln Ile Gln Gly Lys Xaa
Ala Gly Leu Gln Ser Ser Gly Lys Glu Ala Ala Leu Asn Leu Ser Phe
                    45
                                        50
Ile Ser Lys Glu Glu Met Lys Asn Thr Ser Trp Ile Arg Lys Asn Trp
                                    65
Leu Leu Val Ala Gly Ile Ser Phe Ile Gly Asp His Leu Gly Thr Tyr
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Phe Leu Gln Arg Ser Ala Lys Gln Ser Val Lys Phe Gln Ser Gln Ser
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60 65 Lys Met Ile Ala Asn Asp Val His Thr Leu Arg Arg Ser Lys Ala Thr 80 85 Val Gly Arg Pro Leu Ile Ala Trp Arg Tyr Val Pro Ile Asn Val Val 95 100 Glu Thr Leu Arg Thr Arg Gly Ala Pro Thr Arg Ile Val Arg Lys Val 115 Ala Arg Asn Leu Gly Lys Ala Thr Ser Gly Val Leu Val Val Leu Asp 130 Val Val Asn Leu Val Gln Asp Ser Leu Asp Leu His Lys Gly Glu Lys 145 150 Ser Glu Ser Ala Glu Leu Leu Arg Gln Trp Ala Gln Glu Leu Glu Glu 160 165 Asn Leu Asn Glu Leu Thr His Ile His Gln Ser Leu Lys Ala Gly 175

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<210> 148 <211> 180 <212> PRT <213> Homo sapiens

<400> 148 Met Cys Ile Ser Gly Leu Cys Gln Ile Val Gly Cys Asp His Gln Leu 10 Gly Ser Thr Val Lys Glu Asp Asn Cys Gly Val Cys Asn Gly Asp Gly 25 Ser Thr Cys Arg Leu Val Arg Gly Gln Tyr Lys Ser Gln Leu Ser Ala 40 Thr Lys Ser Asp Asp Thr Val Val Ala Ile Pro Tyr Gly Ser Arg His Ile Arg Leu Val Leu Lys Gly Pro Asp His Leu Tyr Leu Glu Thr Lys 70 Thr Leu Gln Gly Thr Lys Gly Glu Asn Ser Leu Ser Ser Thr Gly Thr 85 90 Phe Leu Val Asp Asn Ser Ser Val Asp Phe Gln Lys Phe Pro Asp Lys 100 Glu Ile Leu Arg Met Ala Gly Pro Leu Thr Ala Asp Phe Ile Val Lys 120 Ile Arg Asn Ser Gly Ser Ala Asp Ser Thr Val Gln Phe Ile Phe Tyr

<210> 149

<211> 162 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -23..-1 <400> 149 Met Gly Asp Lys Ile Trp Leu Pro Phe Pro Val Leu Leu Ala Ala -20 -15 Leu Pro Pro Val Leu Leu Pro Gly Ala Ala Gly Phe Thr Pro Ser Leu Asp Ser Asp Phe Thr Phe Thr Leu Pro Ala Gly Gln Lys Glu Cys Phe 15 20 Tyr Gln Pro Met Pro Leu Lys Ala Ser Leu Glu Ile Glu Tyr Gln Val 30 35 Leu Asp Gly Ala Gly Leu Asp Ile Asp Phe His Leu Ala Ser Pro Glu 50 Gly Lys Thr Leu Val Phe Glu Gln Arg Lys Ser Asp Gly Val His Thr Val Glu Thr Glu Val Gly Asp Tyr Met Phe Cys Phe Asp Asn Thr Phe Ser Thr Ile Ser Glu Lys Val Ile Phe Phe Glu Leu Ile Pro Asp Asn 95 100 Met Gly Glu Gln Ala Gln Glu Gln Glu Asp Trp Lys Lys Tyr Ile Thr 110 115 Gly Thr Asp Ile Leu Asp Met Lys Leu Glu Asp Ile Leu Val Ser Met 130 Val Phe

<210> 150
<211> 120
<212> PRT
<213> Homo sapiens
<220>
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<222> -23..-1
<400> 150
Met Gly Asp Lys Ile Trp Leu Pro Phe Pro Val Leu Leu Leu Ala Ala

-20

Leu Pro Pro Val Leu Leu Pro Gly Ala Ala Gly Phe Thr Pro Ser Leu
-5 1 5

Asp Ser Asp Phe Thr Phe Thr Leu Pro Ala Gly Gln Lys Glu Cys Phe
10 15 20 25

Tyr Gln Pro Met Pro Leu Lys Ala Ser Leu Glu Ile Glu Tyr Gln Val

-15

Leu Asp Gly Ala Gly Leu Asp Ile Asp Phe His Leu Ala Ser Pro Glu
45

Gly Lys Thr Leu Val Phe Glu Gln Arg Lys Ser Asp Gly Val His Thr
60

Cys Ile Arg Ser Lys Asn Gly Pro Gly Thr Ala Val His Ala Tyr Asn
75

Pro Ser Thr Phe Arg Gly Gln Val

<210> 151 <211> 7 <212> PRT <213> Homo sapiens <400> 151 Met Val Glu Met Thr Gly Val <210> 152 <211> 199 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -42..-1 <400> 152 Met Asp Gly Gln Lys Lys Asn Trp Lys Asp Lys Val Val Asp Leu Leu -35 -30 Tyr Trp Arg Asp Ile Lys Lys Thr Gly Val Val Phe Gly Ala Ser Leu -20 -15 Phe Leu Leu Ser Leu Thr Val Phe Ser Ile Val Ser Val Thr Ala - 5 1 Tyr Ile Ala Leu Ala Leu Leu Ser Val Thr Ile Ser Phe Arg Ile Tyr 15 Lys Gly Val Ile Gln Ala Ile Gln Lys Ser Asp Glu Gly His Pro Phe 30 Arg Ala Tyr Leu Glu Ser Glu Val Ala Ile Ser Glu Glu Leu Val Gln 45 Lys Tyr Ser Asn Ser Ala Leu Gly His Val Asn Cys Thr Ile Lys Glu 60 Leu Arg Arg Leu Phe Leu Val Asp Asp Leu Val Asp Ser Leu Lys Phe 75 80 Ala Val Leu Met Trp Val Phe Thr Tyr Val Gly Ala Leu Phe Asn Gly 95 100 Leu Thr Leu Leu Ile Leu Ala Leu Ile Ser Leu Phe Ser Val Pro Val 110 115 Ile Tyr Glu Arg His Gln Ala Gln Ile Asp His Tyr Leu Val Leu Ala 125 130 Asn Lys Asn Val Lys Asp Ala Met Ala Lys Ile Gln Ala Lys Ile Pro 140 145 Gly Leu Lys Arg Lys Ala Glu 155

<210> 153

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<211> 43
<212> PRT
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<213> Homo sapiens

<400> 153

Met Pro Phe Arg Met Ser Gly Tyr Ile Pro Phe Gly Thr Pro Ile Val 10 Ser Val Thr Phe Lys Gly Phe Pro Phe Leu Lys Asn Tyr Phe Lys Cys 25 Leu Thr Leu Cys Tyr Cys Ser Arg Val Phe Asp

40

<210> 154

<211> 50

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -37..-1

<400> 154

Met Glu Trp Ala Gly Lys Gln Arg Asp Phe Gln Val Arg Ala Ala Pro -35 -30 -25

Gly Trp Asp His Leu Ala Ser Phe Pro Gly Pro Ser Leu Arg Leu Phe -15

Ser Gly Ser Gln Ala Ser Val Cys Ser Leu Cys Ser Gly Phe Gly Ala

Gln Glu

<210> 155

<211> 153

<212> PRT

<213> Homo sapiens

<400> 155

Thr Val Pro Leu Leu Glu Pro Ala Asp His Ala Arg Gly Arg Ala 10

His Val His Leu Pro Glu Asn Val Arg Ser Gln Ser Pro Gly His Val 25

Arg Arg Gly Arg Ser Gly Ala Gln Val Leu Pro Thr Gly Pro Asp Glu 40 4.5

Lys Gln Val Glu Lys Ser Glu Val Asp Phe Ser Lys Ser His Ser Leu 55

Val Arg Arg Phe Glu Asp Leu Lys Pro Lys Leu Ser Val Cys Lys Thr 70 75

Gly Ser Gln Val Phe Arg Ser Glu Asn Trp Lys Val Trp Ala Glu Ser 90

Ser Arg Gly Asp His Asp Asp Cys Leu Asp Leu Cys Ser Val Leu Cys 105

Trp Gly Glu Leu Leu Arg Thr Ile Pro Glu Ile Pro Pro Lys Arg Gly 120 125

Glu Leu Lys Thr Glu Leu Leu Gly Leu Lys Glu Arg Lys His Lys Pro 135

Gln Val Ser Gln Gln Glu Glu Leu Lys

150

<210> 156 <211> 67 <212> PRT

<213> Homo sapiens

<400> 156

Gly Lys Asp Ile Asp Leu Asn Lys Val Arg Thr Lys Thr Ala Ala Lys
35 40 45

Tyr Gly Leu Ser Ala Gln Pro Arg Leu Val Asp Ile Ile Ala Ala Val 50 55 60

Pro Pro Glu

65

<210> 157

<211> 87

<212> PRT

<213> Homo sapiens

<400> 157

 Met
 Asp
 Glu
 Leu
 Leu
 Ser
 Arg
 Ala
 Arg
 Arg
 Phe
 Leu
 Ser
 Gln
 Pro
 Phe
 Gln
 Val
 Ala
 Glu
 Val
 Phe

 Lys
 Ile
 Gln
 Arg
 Phe
 Leu
 Ser
 Gln
 Pro
 Phe
 Gln
 Val
 Ala
 Glu
 Val
 Phe
 Ala
 Glu
 Val
 Pro
 Leu
 Leu
 Leu
 Leu
 Val
 Pro
 Leu
 Leu
 Leu
 Leu
 Ala
 Glu
 Tyr
 Asp
 His
 Leu
 Pro
 Glu
 Ala
 Asp
 Lys

 Phe
 Tyr
 Met
 Val
 Gly
 Pro
 Ile
 Glu
 Ala
 Val
 Ala
 Lys
 Ala
 Asp
 Lys

 65
 70
 70
 70
 75
 75
 75
 75

Leu Ala Glu Glu His Ser Ser

35

<210> 158

<211> 250

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -85..-1

<400> 158

Met Ser Ala Glu Val Lys Val Thr Gly Gln Asn Gln Glu Gln Phe Leu
-85 -75 -70

Leu Leu Ala Lys Ser Ala Lys Gly Ala Ala Leu Ala Thr Leu Ile His
-65 -60 -55

Gln Val Leu Glu Ala Pro Gly Val Tyr Val Phe Gly Glu Leu Leu Asp
-50
-45
-40

Met Pro Asn Val Arg Glu Leu Xaa Ala Arg Asn Leu Pro Pro Leu Thr
-35 -30 -25

Glu Ala Gln Lys Asn Lys Leu Arg His Leu Ser Val Val Thr Leu Ala
-20 -15 -10

Ala Lys Val Lys Cys Ile Pro Tyr Ala Val Leu Leu Glu Ala Leu Ala

-5 Leu Arg Asn Val Arg Gln Leu Glu Asp Leu Val Ile Glu Ala Val Tyr 15 20 Ala Asp Val Leu Arg Gly Ser Leu Asp Gln Arg Asn Gln Arg Leu Glu Val Asp Tyr Ser Ile Gly Arg Asp Ile Gln Arg Gln Asp Leu Ser Ala 50 Ile Ala Arg Thr Leu Gln Glu Trp Cys Val Gly Cys Glu Val Val Leu 65 70 Ser Gly Ile Glu Glu Gln Val Ser Arg Ala Asn Gln His Lys Glu Gln 85 Gln Leu Gly Leu Lys Gln Gln Ile Glu Ser Glu Val Ala Asn Leu Lys 100 Lys Thr Ile Lys Val Thr Thr Ala Ala Ala Ala Ala Thr Ser Gln 115 120 Asp Pro Glu Gln His Leu Thr Glu Leu Arg Glu Pro Ala Pro Gly Thr 130 135 Asn Gln Arg Gln Pro Ser Lys Lys Ala Ser Lys Gly Lys Gly Leu Arg 145 150 Gly Ser Ala Lys Ile Trp Ser Lys Ser Asn 160

<210> 159 <211> 24

<212> PRT

<213> Homo sapiens

<400> 159

Met Pro Thr Asn Cys Ala Ala Ala Gly Cys Ala Thr Thr Tyr Asn Lys

1 10 15

His Ile Asn Ile Ser Phe His Arg
20

<210> 160

<211> 228

<212> PRT

<213> Homo sapiens

<400> 160

Met Pro Thr Asn Cys Ala Ala Ala Gly Cys Ala Thr Thr Tyr Asn Lys 10 His Ile Asn Ile Ser Phe His Arg Phe Pro Leu Asp Pro Lys Arg Arg 20 25 Lys Glu Trp Val Arg Leu Val Arg Arg Lys Asn Phe Val Pro Gly Lys 40 His Thr Phe Leu Cys Ser Lys His Phe Glu Ala Ser Cys Phe Asp Leu 55 Thr Gly Gln Thr Arg Arg Leu Lys Met Asp Ala Val Pro Thr Ile Phe 70 75 Asp Phe Cys Thr His Ile Lys Ser Met Lys Leu Lys Ser Arg Asn Leu 90 Leu Lys Lys Asn Asn Ser Cys Ser Pro Ala Gly Pro Ser Ser Leu Lys 105 Ser Asn Ile Ser Ser Gln Gln Val Leu Leu Glu His Ser Tyr Ala Phe 120 Arg Asn Pro Met Glu Ala Lys Lys Arg Ile Ile Lys Leu Glu Lys Glu 135 140 Ile Ala Ser Leu Arg Arg Lys Met Lys Thr Cys Leu Gln Lys Glu Arg



<210> 161 <211> 86 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -20..-1 Met Asn Leu His Phe Pro Gln Trp Phe Val His Ser Ser Ala Leu Gly -15 -10 Leu Val Leu Ala Pro Pro Phe Ser Ser Pro Gly Thr Asp Pro Thr Phe Pro Cys Ile Tyr Cys Arg Leu Leu Asn Met Ile Met Thr Arg Leu Ala Phe Ser Phe Ile Thr Cys Leu Cys Pro Asn Leu Lys Glu Val Cys Leu 35 Ile Leu Pro Glu Lys Asn Cys Asn Ser Arg His Ala Gly Phe Val Gly Pro Ala Lys Leu Arg Gln

<210> 163 <211> 314 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -58..-1

<210> 162

<400> 163 Met Gln Asn Val Ile Asn Thr Val Lys Gly Lys Ala Leu Glu Val Ala -55 -50 Glu Tyr Leu Thr Pro Val Leu Lys Glu Ser Lys Phe Arg Glu Thr Gly -35 Val Ile Thr Pro Glu Glu Phe Val Ala Ala Gly Asp His Leu Val His -20 -15 His Cys Pro Thr Trp Gln Trp Ala Thr Gly Glu Glu Leu Lys Val Lys Ala Tyr Leu Pro Thr Gly Lys Gln Phe Leu Val Thr Lys Asn Val Pro 15 Cys Tyr Lys Arg Cys Lys Gln Met Glu Tyr Ser Asp Glu Leu Glu Ala 30 Ile Ile Glu Glu Asp Asp Gly Asp Gly Trp Val Asp Thr Tyr His 45 Asn Thr Gly Ile Thr Gly Ile Thr Glu Ala Val Lys Glu Ile Thr Leu 60 65 Glu Asn Lys Asp Asn Ile Arg Leu Gln Asp Cys Ser Ala Leu Cys Glu 75 80 Glu Glu Glu Asp Glu Asp Glu Gly Glu Ala Ala Asp Met Glu Glu Tyr 95 Glu Glu Ser Gly Leu Leu Glu Thr Asp Glu Ala Thr Leu Asp Thr Arg 110 Lys Ile Val Glu Ala Cys Lys Ala Lys Thr Asp Ala Gly Gly Glu Asp 125 130 Ala Ile Leu Gln Thr Arg Thr Tyr Asp Leu Tyr Ile Thr Tyr Asp Lys 140 145 Tyr Tyr Gln Thr Pro Arg Leu Trp Leu Phe Gly Tyr Asp Glu Gln Arg 155 160 Gln Pro Leu Thr Val Glu His Met Tyr Glu Asp Ile Ser Gln Asp His 170 175 Val Lys Lys Thr Val Thr Ile Glu Asn His Pro His Leu Pro Pro 190 195 Pro Met Cys Ser Val His Pro Cys Arg His Ala Glu Val Met Lys Lys 205 210 Ile Ile Glu Thr Val Ala Glu Gly Gly Glu Leu Gly Val His Met 220 225 Tyr Leu Leu Ile Phe Leu Lys Phe Val Gln Ala Val Ile Pro Thr Ile 235 240 Glu Tyr Asp Tyr Thr Arg His Phe Thr Met

<210> 164 <211> 89 <212> PRT <213> Homo sapiens <220>

<221> SIGNAL <222> -80..-1

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-30 -25 -20

Gln Leu Gly Arg Gly Leu Leu Ser Ala Cys Ala Pro Trp Gly Asp Gly
-15 -10 -5

Ser Thr Gln Pro Val Pro Leu Cys Ser
1 5
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<210> 165 <211> 98 <212> PRT <213> Homo sapiens

<221> SIGNAL <222> -15..-1

<220>

Thr Ala

<210> 166 <211> 92 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -36..-1

<210> 167
<211> 351
<212> PRT

<213> Homo sapiens

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<220>

<221> SIGNAL

<222> -16..-1

<400> 167

Met Val Pro Phe Ile Tyr Leu Gln Ala His Phe Thr Leu Cys Ser Gly -10

Trp Ser Ser Thr Tyr Arg Asp Leu Arg Lys Gly Val Tyr Val Pro Tyr 10

Thr Gln Gly Lys Trp Glu Gly Glu Leu Gly Thr Asp Leu Val Ser Ile

Pro His Gly Pro Asn Val Thr Val Arg Ala Asn Ile Ala Ala Ile Thr 40

Glu Ser Asp Lys Phe Phe Ile Asn Gly Ser Asn Trp Glu Gly Ile Leu 55

Gly Leu Ala Tyr Ala Glu Ile Ala Arg Pro Asp Asp Ser Pro Glu Pro 70 75

Phe Phe Asp Ser Leu Val Lys Gln Thr His Val Pro Asn Leu Phe Ser 85 90

Leu Gln Leu Cys Gly Ala Gly Phe Pro Leu Asn Gln Ser Glu Val Leu 100 105

Ala Ser Val Gly Gly Ser Met Ile Ile Gly Gly Ile Asp His Ser Leu 120

Tyr Thr Gly Ser Leu Trp Tyr Thr Pro Ile Arg Arg Glu Trp Tyr Tyr 135

Glu Val Ile Ile Val Arg Val Glu Ile Asn Gly Gln Asp Leu Lys Met 150 155

Asp Cys Lys Glu Tyr Asn Tyr Asp Lys Ser Ile Val Asp Ser Gly Thr 165 170

Thr Asn Leu Arg Leu Pro Lys Lys Val Phe Glu Ala Ala Val Lys Ser 180 185

Ile Lys Ala Ala Ser Ser Thr Glu Lys Phe Pro Asp Gly Phe Trp Leu 200

205 Gly Glu Gln Leu Val Cys Trp Gln Ala Gly Thr Thr Pro Trp Asn Ile

215 220 Phe Pro Val Ile Ser Leu Tyr Leu Met Gly Glu Val Thr Asn Gln Ser 230 235

Phe Arg Ile Thr Ile Leu Pro Gln Gln Tyr Leu Arg Pro Val Glu Asp 245 250

Val Ala Thr Ser Gln Asp Asp Cys Tyr Lys Phe Ala Ile Ser Gln Ser 260 265 - 270

Ser Thr Gly Thr Val Met Gly Ala Val Ile Met Glu Gly Phe Tyr Val 275 280 285

Val Phe Asp Arg Ala Arg Lys Arg Ile Gly Phe Ala Val Ser Ala Cys 295 300

His Val His Asp Glu Phe Arg Thr Ala Ala Val Glu Gly Pro Phe Cys 310 315

His Leu Gly His Gly Arg Leu Trp Leu Gln His Ser Thr Asp Arg

<210> 168

<211> 138

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -47..-1



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<400> 168
Met Glu Lys Phe Val Asp Pro Gly Asn His Asn Ser Gly Ile Asp Leu
                            -40
Leu Arg Thr Tyr Leu Trp Arg Cys Gln Phe Leu Leu Pro Phe Val Ser
                        -25
```

Leu Gly Leu Met Cys Phe Gly Ala Leu Ile Gly Leu Cys Ala Cys Ile -10

Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly Ile Leu His Leu Leu

Ala Gly Leu Cys Thr Leu Gly Ser Val Ser Cys Tyr Val Ala Gly Ile 20 25

Glu Leu Leu His Gln Lys Leu Glu Leu Pro Asp Asn Val Ser Gly Glu 45

Phe Gly Trp Ser Phe Cys Leu Ala Cys Val Ser Ala Pro Leu Gln Phe 55 60

Met Ala Ser Ala Leu Phe Ile Trp Ala Ala His Thr Asn Arg Arg Glu 75

Tyr Thr Leu Met Lys Ala Tyr Arg Val Ala

<210> 169

<211> 101

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -73..-1

<400> 169

Met Asn Leu Glu Arg Val Ser Asn Glu Glu Lys Leu Asn Leu Cys Arg -65

Lys Tyr Tyr Leu Gly Gly Phe Ala Phe Leu Pro Phe Leu Trp Leu Val -55 -50

Asn Ile Phe Trp Phe Tyr Arg Glu Ala Phe Leu Val Pro Ala Tyr Thr -35 -30

Glu Gln Ser Gln Ile Lys Gly Tyr Val Trp Arg Ser Ala Val Gly Phe -15

Leu Phe Trp Val Ile Val Leu Thr Ser Trp Ile Thr Ile Phe Gln Ile 1

Tyr Arg Pro Arg Trp Gly Ala Leu Gly Asp Tyr Leu Ser Phe Thr Ile 10

Pro Leu Gly Thr Pro 25

<210> 170

<211> 252

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -68..-1

<400> 170

Met Pro Glu Gly Pro Glu Leu His Leu Ala Ser Gln Phe Val Asn Glu

-60

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Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val -50 -45 -40 Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser -30 -25 Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro -15 -10 Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His 15 20 Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu 35 Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 50 60 Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe Arg Glu Asn Val Leu Arg Asn Leu Ala Asp Lys Ala Phe Asp Arg Pro Ile Cys Glu Ala Leu Leu Asp Gln Arg Phe Phe Asn Gly Ile Gly Asn 100 105 Tyr Leu Arg Ala Glu Ile Leu Tyr Arg Leu Lys Ile Pro Pro Phe Glu 115 120 Lys Ala Arg Ser Val Leu Glu Ala Leu Gln Gln His Arg Pro Ser Pro 130 135 Glu Leu Thr Leu Ser Gln Lys Ile Arg Thr Lys Leu Gln Asn Ser Asp 150 Leu Leu Glu Leu Cys His Ser Val Pro Lys Glu Val Val Gln Leu Gly 165 Glu Ala Lys Asp Gly Ser Asn Leu Cys Phe Ser Lys 180

<210> 171
<211> 350
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -68..-1

<400> 171 Met Pro Glu Gly Pro Glu Leu His Leu Ala Ser Gln Phe Val Asn Glu -60 Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val -45 -50 -40 Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser -30 -25 Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro -15 -10 Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly 5 Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His 20 Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu 35 Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 50 55 Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe 70 Arg Leu Lys Ile Pro Pro Phe Glu Lys Ala Arg Ser Val Leu Glu Ala



85 Leu Gln Gln His Arg Pro Ser Pro Glu Leu Thr Leu Ser Gln Lys Ile 100 105 Arg Thr Lys Leu Gln Asn Pro Asp Leu Leu Glu Leu Cys His Ser Val 115 Pro Lys Glu Val Asp Gln Leu Gly Gly Arg Gly Tyr Gly Ser Glu Ser 130 135 Gly Glu Glu Asp Phe Ala Ala Phe Arg Ala Trp Leu Arg Cys Tyr Gly 145 150 Met Pro Gly Met Ser Ser Leu Gln Asp Arg His Gly Arg Thr Ile Trp 165 170 Phe Gln Gly Asp Pro Gly Pro Leu Ala Pro Lys Gly Arg Lys Ser Arg 175 180 Lys Lys Lys Ser Lys Ala Thr Gln Leu Ser Pro Glu Asp Arg Val Glu 195 200 Asp Ala Leu Pro Pro Ser Lys Ala Pro Ser Lys Thr Arg Arg Ala Lys 210 215 Arg Asp Leu Pro Lys Arg Thr Ala Thr Gln Arg Pro Glu Gly Thr Ser 225 230 Leu Gln Gln Asp Pro Glu Ala Pro Thr Val Pro Lys Lys Gly Arg Arg 240 245 Lys Gly Arg Gln Ala Ala Ser Gly His Cys Arg Pro Arg Lys Val Lys 260 Ala Asp Ile Pro Ser Leu Glu Pro Glu Gly Thr Ser Ala Ser 275

<210> 172 <211> 390 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -68..-1 <400> 172

Met Pro Glu Gly Pro Glu Leu His Leu Ala Ser Gln Phe Val Asn Glu -60 Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val -45 Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser -30 -25 Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro -15 -10 Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His 20 Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu 35 40 Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 50 Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe 70 Arg Glu Asn Val Leu Arg Asn Leu Ala Asp Lys Ala Phe Asp Arg Pro 85 Ile Cys Glu Ala Leu Leu Asp Gln Arg Phe Phe Asn Gly Ile Gly Asn 100 105 Tyr Leu Arg Ala Glu Ile Leu Tyr Arg Leu Lys Ile Pro Pro Phe Glu 115

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Lys Ala Arg Ser Val Leu Glu Ala Leu Gln Gln His Arg Pro Ser Pro 130 135 Glu Leu Thr Leu Ser Gln Lys Ile Arg Thr Lys Leu Gln Asn Pro Asp 150 145 Leu Leu Glu Leu Cys His Ser Val Pro Lys Glu Val Val Gln Leu Gly 160 165 170 Gly Arg Gly Tyr Gly Ser Glu Ser Gly Glu Glu Asp Phe Ala Ala Phe 175 180 185 Arg Ala Trp Leu Arg Cys Tyr Gly Met Pro Gly Met Ser Ser Leu Gln 195 200 Asp Arg His Gly Arg Thr Ile Trp Phe Gln Gly Asp Pro Gly Pro Leu 210 215 Ala Pro Lys Gly Arg Lys Ser Arg Lys Lys Lys Ser Lys Ala Thr Gln 225 230 Leu Ser Pro Glu Asp Arg Val Glu Asp Ala Leu Pro Pro Ser Lys Ala 240 245 Pro Ser Arg Thr Arg Arg Ala Lys Arg Asp Leu Pro Lys Arg Thr Ala 260 265 Thr Gln Arg Pro Glu Gly Thr Ser Leu Gln Gln Asp Pro Glu Ala Pro 275 280 Thr Val Pro Lys Lys Gly Arg Arg Lys Gly Arg Gln Ala Ala Ser Gly 290 295 His Cys Arg Pro Arg Lys Val Lys Ala Asp Ile Pro Ser Leu Glu Pro 305 310 Glu Gly Thr Ser Ala Ser 320

<210> 173 <211> 190 <212> PRT <213> Homo sapiens <220>

<221> SIGNAL <222> -82..-1

<400> 173 Met Tyr Val Trp Pro Cys Ala Val Val Leu Ala Gln Tyr Leu Trp Phe -75 His Arg Arg Ser Leu Pro Gly Lys Ala Ile Leu Glu Ile Gly Ala Gly -60 -55 Val Ser Leu Pro Gly Ile Leu Thr Ala Lys Cys Gly Ala Glu Val Ile -45 -40 Leu Ser Asp Ser Ser Glu Leu Pro His Cys Leu Glu Val Cys Arg Gln -30 -25 Ser Cys Gln Met Asn Asn Leu Pro His Leu Gln Val Val Gly Leu Thr -10 - 5 -15 Trp Gly His Ile Ser Trp Asp Leu Leu Ala Leu Pro Pro Gln Asp Ile Ile Leu Ala Ser Asp Val Phe Phe Glu Pro Glu Asp Phe Glu Asp Ile 20 25 Leu Ala Thr Ile Tyr Phe Leu Met His Lys Asn Pro Lys Val Gln Leu 35 40 Trp Ser Thr Tyr Gln Val Arg Ser Ala Asp Trp Ser Leu Glu Ala Leu 55 Leu Tyr Lys Trp Asp Met Lys Cys Val His Ile Pro Leu Glu Ser Phe 70 75 Asp Ala Asp Lys Glu Asp Ile Ala Glu Ser Thr Leu Pro Gly Arg His 85 90 Thr Val Glu Met Leu Val Ile Ser Phe Ala Lys Asp Ser Leu

<210> 174 <211> 285 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -232..-1

<400> 174 Met Gly Cys Val Phe Gln Ser Thr Glu Asp Lys Arg Ile Phe Lys Ile -230 -225 -220 Asp Trp Thr Leu Ser Pro Gly Glu His Ala Lys Asp Glu Tyr Val Leu -215 -210 -205 Tyr Tyr Tyr Ser Asn Leu Ser Val Pro Ile Gly Arg Phe Gln Asn Arg -200 -195 -190 Val His Leu Met Gly Asp Asn Leu Cys Asn Asp Gly Ser Leu Leu -180 -175 Gln Asp Val Gln Glu Ala Asp Gln Gly Thr Tyr Ile Cys Glu Ile Arg -165 -160 -155 Leu Lys Gly Glu Ser Gln Val Phe Lys Lys Ala Val Val Leu His Val -150 -145 -140 Leu Pro Glu Glu Pro Lys Glu Leu Met Val His Val Gly Gly Leu Ile -130 -125 Gln Met Gly Cys Val Phe Gln Ser Thr Glu Val Lys His Val Thr Lys -115 -110 Val Glu Trp Ile Phe Ser Gly Arg Arg Ala Lys Glu Glu Ile Val Phe -100 - 95 -90 Arg Tyr Tyr His Lys Leu Arg Met Ser Ala Glu Tyr Ser Gln Ser Trp -80 Gly His Phe Gln Asn Arg Val Asn Leu Val Gly Asp Ile Phe Arg Asn -70 -65 Asp Gly Ser Ile Met Leu Gln Gly Val Arg Glu Ser Asp Gly Gly Asn -50 -45 Tyr Thr Cys Ser Ile His Leu Gly Asn Leu Val Phe Lys Lys Thr Ile -35 -30 Val Leu His Val Ser Pro Glu Glu Pro Arg Thr Leu Val Thr Pro Ala -20 -15 Ala Leu Arg Pro Leu Val Leu Gly Gly Asn Gln Leu Val Ile Ile Val 1 Gly Ile Val Cys Ala Thr Ile Leu Leu Leu Pro Val Leu Ile Leu Ile 15 20 Val Lys Lys Thr Cys Gly Asn Lys Ser Ser Val Asn Ser Thr Val Leu 30 35 Val Lys Asn Thr Lys Lys Thr Asn Pro Lys Lys Lys

<210> 175

<211> 153

<212> PRT

<213> Homo sapiens

4.5

<400> 175

Met Gly Cys Val Phe Gln Ser Thr Val Asp Lys Cys Ile Phe Lys Ile 10 15 Asp Trp Thr Leu Ser Pro Gly Glu His Ala Lys Asp Glu Tyr Val Leu



20 Tyr Tyr Tyr Ser Asn Leu Ser Val Pro Ile Gly Arg Phe Gln Asn Arg 40 35 Val His Leu Met Gly Asp Ile Leu Cys Asn Asp Gly Ser Leu Leu Leu Gln Asp Val Gln Glu Ala Asp Gln Gly Thr Tyr Ile Cys Glu Ile Arg Leu Lys Gly Glu Ser Gln Val Phe Lys Lys Ala Val Val Leu His Val 90 Leu Pro Glu Glu Pro Lys Glu Leu Met Val His Val Gly Gly Leu Ile 105 110 Gln Met Gly Cys Val Phe Gln Ser Thr Glu Val Lys His Val Thr Lys 120 Val Glu Trp Ile Phe Ser Gly Arg Arg Ala Lys Val Thr Arg Arg Lys 135 His His Cys Val Arg Glu Gly Ser Gly 150

<210> 176 <211> 49 <212> PRT <213> Homo sapiens

<210> 177
<211> 99
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -24..-1

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<210> 178
<211> 95
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 178
Met Ala Ser Pro Ala Val Asn Arg Trp Lys Arg Pro Arg Leu Lys Pro
                            -30
Val Trp Pro Arg Arg Leu Glu Ser Trp Leu Leu Leu Asp Ala Leu Leu
                                            -10
Arg Leu Gly Asp Thr Lys Lys Lys Arg Gln Pro Glu Ala Ala Thr Lys
Ser Cys Val Arg Ser Ser Cys Gly Gly Pro Ser Gly Asp Gly Pro Pro
                                20
Pro Cys Leu Gln Gln Pro Asp Pro Arg Ala Leu Ser Gln Ala Phe Ser
                           35
Arg Ser Phe Pro Leu Phe Pro Ser Leu Ala Gly Lys Ser Met Ile
<210> 179
<211> 121
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<210> 180
<211> 59
<212> PRT
<213> Homo sapiens
<400> 180
Met Ile Leu Cys Phe Leu Leu Pro His His Arg Leu Gln Glu Ala Arg
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10 15
Gln Ile Gln Val Leu Lys Met Leu Pro Arg Glu Lys Leu Arg Arg Arg 20 25 30
Glu Glu Arg Lys Gln Ile Asn Gly Lys Lys Glu Arg Thr Lys Tyr Glu 35 40 45
Thr Pro Arg Lys Arg Glu Gly Lys Lys Lys Lys Lys 50 55
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<210> 181 <211> 86 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -14..-1

<210> 182 <211> 165 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -58..-1

<400> 182

70

Met Thr Arg Leu Cys Leu Pro Arg Pro Glu Ala Arg Glu Asp Pro Ile -55 -50 Pro Val Pro Pro Arg Gly Leu Gly Ala Gly Glu Gly Ser Gly Ser Pro -35 Val Arg Pro Pro Val Ser Thr Trp Gly Pro Ser Trp Ala Gln Leu Leu -20 -15 Asp Ser Val Leu Trp Leu Gly Ala Leu Gly Leu Thr Ile Gln Ala Val -5 Phe Ser Thr Thr Gly Pro Ala Leu Leu Leu Leu Val Ser Phe Leu 15 20 Thr Phe Asp Leu Leu His Arg Pro Ala Gly His Thr Leu Pro Gln Arg 30 Lys Leu Leu Thr Arg Gly Gln Ser Gln Gly Ala Gly Glu Gly Pro Gly 45 Gln Gln Glu Ala Leu Leu Gln Met Gly Thr Val Ser Gly Gln Leu 60 Ser Leu Gln Asp Ala Leu Leu Leu Leu Met Gly Leu Gly Pro Leu



Leu Arg Ala Cys Gly Met Pro Leu Thr Leu Leu Gly Leu Ala Phe Cys 90 95 100

Leu His Pro Trp Ala 105

 Cys
 Asn
 Gly
 Lys
 Glu
 Met
 Ser
 Pro
 Thr
 Arg
 Gln
 Leu
 Arg
 Cys
 Pro
 Pro

 Gly
 Ser
 His
 Cys
 Leu
 Thr
 Ile
 Thr
 Asp
 Val
 Pro
 Val
 Thr
 V

<210> 184 <211> 73 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1

<400> 184

 Met Ala Pro Gln Thr Leu Leu Pro Val Leu Val Leu Cys Val Leu Leu -20
 -15
 -10

 Leu Gln Ala Gln Gly Gly Tyr Arg Asp Lys Met Arg Met Gln Arg Ile -5
 5
 10

 Lys Val Cys Glu Lys Arg Pro Ser Ile Asp Leu Cys Ile His His Cys 15
 20
 25

 Ser Cys Phe Gln Lys Cys Glu Thr Asn Lys Ile Cys Cys Ser Ala Phe 30
 35
 40

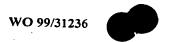
Cys Gly Asn Ile Cys Met Ser Ile Leu 45 50

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<211> 98
<212> PRT
<213> Homo sapiens
<400> 185
Met Leu Gly Ala Glu Thr Glu Glu Lys Leu Phe Asp Ala Pro Leu Ser
1 5 10 15



<210> 186 <211> 112 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1

<210> 187
<211> 70
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -44..-1



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<211> 92
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<221> SIGNAL
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<222> -13..-1

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<210> 189
<211> 207
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -42..-1
<400> 189
Met His Ile Leu Gln Leu Leu Thr Thr Val Asp Asp Gly Ile Gln Ala
                          -35
Ile Val His Cys Pro Asp Thr Gly Lys Asp Ile Trp Asn Leu Leu Phe
                       -20
                                          -15
Asp Leu Val Cys His Glu Phe Cys Gln Ser Asp Asp Pro Pro Ile Ile
                   - 5
Leu Gln Glu Gln Lys Thr Val Leu Ala Ser Val Phe Ser Val Leu Ser
Ala Ile Tyr Ala Ser Gln Thr Glu Gln Glu Tyr Leu Lys Ile Glu Lys
                          30
Val Asp Leu Pro Leu Ile Asp Ser Leu Ile Arg Val Leu Gln Asn Met
                       45
Glu Gln Cys Gln Lys Lys Pro Glu Asn Ser Ala Glu Ser Asn Thr Glu
                   60
                                      65
Glu Thr Lys Arg Thr Asp Leu Thr Gln Asp Asp Leu His Leu Lys Ile
 Leu Lys Asp Ile Leu Cys Glu Phe Leu Ser Asn Ile Phe Gln Ala Leu
Thr Lys Glu Thr Val Ala Gln Gly Val Lys Glu Gly Gln Leu Ser Lys
                          110
                                             115
Gln Lys Cys Ser Ser Ala Phe Gln Asn Leu Leu Pro Phe Tyr Ser Pro
   120
                      125
                                          130
Val Val Glu Asp Phe Ile Lys Ile Leu Arg Glu Val Asp Lys Ala Leu
                   140
                                      145
Ala Asp Asp Leu Glu Lys Asn Phe Pro Ser Leu Lys Val Gln Thr
```

160

165

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<210> 190
<211> 201
<212> PRT
<213> Homo sapiens
<400> 190
Met Gln Val Ala Leu Lys Glu Asp Leu Asp Ala Leu Lys Glu Lys Phe
                                    10
Arg Thr Met Glu Ser Asn Gln Lys Ser Ser Phe Gln Glu Ile Pro Lys
                                25
Leu Asn Glu Glu Leu Leu Ser Lys Gln Lys Gln Leu Glu Lys Ile Glu
                            40
Ser Gly Glu Met Gly Leu Asn Lys Val Trp Ile Asn Ile Thr Glu Met
                       55
Asn Lys Gln Ile Ser Leu Leu Thr Ser Ala Val Asn His Leu Lys Ala
                   70
                                       75
Asn Val Lys Ser Ala Ala Asp Leu Ile Ser Leu Pro Thr Thr Val Glu
               85
                                    90
Gly Leu Gln Lys Ser Val Ala Ser Ile Gly Asn Thr Leu Asn Ser Val
           100
                               105
His Leu Ala Val Glu Ala Leu Gln Lys Thr Val Asp Glu His Lys Lys
                           120
                                               125
Thr Met Glu Leu Gln Ser Asp Met Asn Gln His Phe Leu Lys Glu
                       135
                                           140
Thr Pro Gly Ser Asn Gln Ile Ile Pro Ser Pro Ser Ala Thr Ser Glu
                   150
                                       155
Leu Asp Asn Lys Thr His Ser Glu Asn Leu Lys Gln Met Gly Asp Arg
               165
                                   170
Ser Ala Thr Leu Lys Arg Gln Ser Leu Asp Gln Val Thr Asn Arg Thr
           180
                                185
Asp Thr Val Lys Ile Gln Lys Lys
       195
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<211> 379
<212> PRT
<213> Homo sapiens
<220>
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<222> -37..-1
<400> 191
Met Pro His Ser Ser Leu His Pro Ser Ile Pro Cys Pro Arg Gly His
       -35
                            -30
                                                -25
Gly Ala Gln Lys Ala Ala Leu Val Leu Leu Ser Ala Cys Leu Val Thr
                        -15
                                            -10
Leu Trp Gly Leu Gly Glu Pro Pro Glu His Thr Leu Arg Tyr Leu Val
Leu His Leu Ala Ser Leu Gln Leu Gly Leu Leu Asn Gly Val Cys
                                20
Ser Leu Ala Glu Glu Leu Arg His Ile His Ser Arg Tyr Arg Gly Ser
                            35
```

Tyr Trp Arg Thr Val Arg Ala Cys Leu Gly Cys Pro Leu Arg Arg Gly

Ala Leu Leu Leu Ser Ile Tyr Phe Tyr Tyr Ser Leu Pro Asn Ala

50

<210> 191



60 70 Val Gly Pro Pro Phe Thr Trp Met Leu Ala Leu Leu Gly Leu Ser Gln 80 Ala Leu Asn Ile Leu Leu Gly Leu Lys Gly Leu Ala Pro Ala Glu Ile 100 Ser Ala Val Cys Glu Lys Gly Asn Phe Asn Val Ala His Gly Leu Ala 115 Trp Ser Tyr Tyr Ile Gly Tyr Leu Arg Leu Ile Leu Pro Glu Leu Gln 130 135 Ala Arg Ile Arg Thr Tyr Asn Gln His Tyr Asn Asn Leu Leu Arg Gly 145 150 Ala Val Ser Gln Arg Leu Tyr Ile Leu Leu Pro Leu Asp Cys Gly Val 160 165 Pro Asp Asn Leu Ser Met Ala Asp Pro Asn Ile Arg Phe Leu Asp Lys 180 Leu Pro Gln Gln Thr Gly Asp Arg Ala Gly Ile Lys Asp Arg Val Tyr 195 Ser Asn Ser Ile Tyr Glu Leu Leu Glu Asn Gly Gln Arg Ala Gly Thr 210 215 Cys Val Leu Glu Tyr Ala Thr Pro Leu Gln Thr Leu Phe Ala Met Ser 220 225 230 Gln Tyr Ser Gln Ala Gly Phe Ser Arg Glu Asp Arg Leu Glu Gln Ala 240 245 Lys Leu Phe Cys Arg Thr Leu Glu Asp Ile Leu Ala Asp Ala Pro Glu 260 Ser Gln Asn Asn Cys Arg Leu Ile Ala Tyr Gln Glu Pro Ala Asp Asp 275 Ser Ser Phe Ser Leu Ser Gln Glu Val Leu Arg His Leu Arg Gln Glu 290 295 Glu Lys Glu Glu Val Thr Val Gly Ser Leu Lys Thr Ser Ala Val Pro 305 310 Ser Thr Ser Thr Met Ser Gln Glu Pro Glu Leu Leu Ser Gly Met 320 325 Gly Lys Pro Leu Pro Leu Arg Thr Asp Phe Ser

<210> 192 <211> 112

<212> PRT

<213> Homo sapiens

<400> 192

 Met
 Pro
 Ser
 Glu
 Gly
 Arg
 Cys
 Trp
 Glu
 Thr
 Leu
 Lys
 Ala
 Leu
 Arg
 Ser

 Ser
 Asp
 Lys
 Gly
 Arg
 Leu
 Cys
 Tyr
 Tyr
 Arg
 Asp
 Trp
 Leu
 Arg
 Arg

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<211> 43
<212> PRT
<213> Homo sapiens
<400> 193
Ser Leu Pro Gln Ala Leu Trp Phe Gln Phe Phe Tyr His Ser Gly Ser
Ser Leu Glu Ser Pro Gly Met Leu Asn Gly Pro Phe Gln His Arg Asn
           20
                                25
Ser Arg Ile Met Thr His Arg Ser Ala Glu Lys
<210> 194
<211> 51
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 194
Met Leu Arg Ile Ala Leu Thr Leu Ile Pro Ser Met Leu Ser Arg Ala
                       -10
Ala Gly Trp Cys Trp Tyr Lys Glu Pro Thr Gln Gln Phe Ser Tyr Leu
                                    10
Cys Leu Pro Cys Leu Ser Trp Asn Lys Lys Gly Asn Val Leu Gln Leu
                                25
Pro Asn Phe
       35
<210> 195
<211> 244
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -18..-1
<400> 195
Met Ala Asn Pro Lys Leu Gly Leu Glu Leu Ser Glu Ala Glu Ala
           -15
                                -10
Ile Gly Ala Asp Ser Ala Arg Phe Glu Glu Leu Leu Gln Ala Ser
                                            10
Lys Glu Leu Gln Gln Ala Gln Thr Thr Arg Pro Glu Ser Thr Gln Ile
                   20
                                        25
Gln Pro Gln Pro Gly Phe Cys Ile Lys Thr Asn Ser Ser Glu Gly Lys
Val Phe Ile Asn Ile Cys His Ser Pro Ser Ile Pro Pro Pro Ala Asp
Val Thr Glu Glu Leu Leu Gln Met Leu Glu Glu Asp Gln Ala Gly
                            70
Phe Arg Ile Pro Met Ser Leu Gly Glu Pro His Ala Glu Leu Asp Ala
```

Lys Gly Gln Gly Cys Thr Ala Tyr Asp Val Ala Val Asn Ser Asp Phe

Tyr Arg Arg Met Gln Asn Ser Asp Phe Leu Arg Glu Leu Val Ile Thr

90



115 120 Ile Ala Arg Glu Gly Leu Glu Asp Ile Tyr Asn Leu Gln Leu Asn Pro 130 135 Glu Trp Arg Met Met Lys Asn Arg Pro Phe Met Gly Ser Ile Ser Gln 150 Gln Asn Ile Arg Ser Glu Gln Arg Pro Arg Ile Gln Glu Leu Gly Asp 165 170 Leu Tyr Thr Pro Ala Pro Gly Arg Ala Glu Ser Gly Pro Glu Lys Pro 180 185 His Leu Asn Leu Trp Leu Glu Ala Pro Asp Leu Leu Leu Ala Glu Val 195 200 Asp Leu Pro Lys Leu Asp Gly Ala Leu Gly Leu Ser Leu Glu Ile Gly 215 Arg Thr Ala Trp

<210> 196 <211> 353 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -34..-1

225

<400> 196 Met Glu Arg Gly Leu Lys Ser Ala Asp Pro Arg Asp Gly Thr Gly Tyr -30 -25 Thr Gly Trp Ala Gly Ile Ala Val Leu Tyr Leu His Leu Tyr Asp Val -10 Phe Gly Asp Pro Ala Tyr Leu Gln Leu Ala His Gly Tyr Val Lys Gln Ser Leu Asn Cys Leu Thr Lys Arg Ser Ile Thr Phe Leu Cys Gly Asp 20 Ala Gly Pro Leu Ala Val Ala Val Leu Tyr His Lys Met Asn Asn 40 Glu Lys Gln Ala Glu Asp Cys Ile Thr Arg Leu Ile His Leu Asn Lys Ile Asp Pro His Ala Pro Asn Glu Met Leu Tyr Gly Arg Ile Gly Tyr 70 Ile Tyr Ala Leu Leu Phe Val Asn Lys Asn Phe Gly Val Glu Lys Thr 85 90 Pro Gln Ser His Ile Gln Gln Ile Cys Glu Thr Ile Leu Thr Ser Gly 100 105 Glu Asn Leu Ala Arg Lys Arg Asn Phe Thr Ala Lys Ser Pro Leu Met 115 120 Tyr Glu Trp Tyr Gln Glu Tyr Tyr Val Gly Ala Ala His Gly Leu Ala 130 135 Gly Ile Tyr Tyr Tyr Leu Met Gln Pro Ser Leu Gln Val Ser Gln Gly 150 155 Lys Leu His Ser Leu Val Lys Pro Ser Val Asp Tyr Val Cys Gln Leu 165 170 Lys Phe Pro Ser Gly Asn Tyr Pro Pro Cys Ile Gly Asp Asn Arg Asp 185 190 Leu Leu Val His Trp Cys His Gly Ala Pro Gly Val Ile Tyr Met Leu 195 200 Ile Gln Ala Tyr Lys Val Phe Arg Glu Glu Lys Tyr Leu Cys Asp Ala 210 215 Tyr Gln Cys Ala Asp Val Ile Trp Gln Tyr Gly Leu Leu Lys Lys Gly **2**25 230



Tyr Gly Leu Cys His Gly Ser Ala Gly Asn Ala Tyr Ala Phe Leu Thr 245 Leu Tyr Asn Leu Thr Gln Asp Met Lys Tyr Leu Tyr Arg Ala Cys Lys 260 265 Phe Ala Glu Trp Cys Leu Glu Tyr Gly Glu His Gly Cys Arg Thr Pro 275 280

Asp Thr Pro Phe Ser Leu Phe Glu Gly Met Ala Gly Thr Ile Tyr Phe 290 295 Leu Ala Asp Leu Leu Val Pro Thr Lys Ala Arg Phe Pro Ala Phe Glu

310

Leu

<210> 197 <211> 30

<212> PRT

<213> Homo sapiens

<400> 197

Met Gln Met Asp Thr Phe Phe Met Ser Glu Lys His Thr His Thr His 5 10 Thr His Ile His Thr His Thr Arg Lys Thr Lys Lys Lys 25

<210> 198

<211> 112

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -48..-1

<400> 198

Met Gln Asp Thr Gly Ser Val Val Pro Leu His Trp Phe Gly Phe Gly -40

Tyr Ala Ala Leu Val Ala Ser Gly Gly Ile Ile Gly Tyr Val Lys Ala -30 -25 -20

Gly Ser Val Pro Ser Leu Ala Ala Gly Leu Leu Phe Gly Ser Leu Ala -10 -5

Gly Leu Gly Ala Tyr Gln Leu Ser Gln Asp Pro Arg Asn Val Trp Val

Phe Leu Ala Thr Ser Gly Thr Leu Ala Gly Ile Met Gly Met Arg Phe 25

Tyr His Ser Gly Lys Phe Met Pro Ala Gly Leu Ile Ala Gly Ala Ser 40

Leu Leu Met Val Ala Lys Val Gly Val Ser Met Phe Asn Arg Pro His

<210> 199

<211> 54

<212> PRT

<213> Homo sapiens

<400> 199

Glu Ile Ala Gly Tyr Gly Ala Glu Gly Phe Ser Ser Val Leu Gly Tyr 10

<210> 200



 Pro Arg Trp His Arg Leu Pro Pro Gln Ser Leu Gln His His Gln Tyr

 20
 25
 30

 Cys Gln Arg Arg Trp Pro Asp Arg Arg Cys Leu Gln Ser His Thr Gln
 35
 40

 Ser Ser Gly His Leu Pro
 50

<211> 151 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1 <400> 200 Met Ala Ala Ser Thr Ser Met Xaa Pro Val Ala Val Thr Ala Ala Val -15 Ala Pro Val Leu Ser Ile Asn Ser Asp Phe Ser Asp Leu Arg Glu Ile 5 1 Lys Lys Gln Leu Leu Leu Ile Ala Gly Leu Thr Arg Glu Arg Gly Leu 20 Leu His Ser Ser Lys Trp Ser Ala Glu Leu Ala Phe Ser Leu Pro Ala 35 Leu Pro Xaa Gly Gln Leu Gln Pro Pro Pro Pro Ile Thr Glu Glu Asp 50 . .55 Ala Gln Asp Met Asp Ala Tyr Thr Leu Ala Lys Ala Tyr Phe Asp Val 65 Lys Glu Tyr Asp Arg Ala Ala His Phe Leu His Gly Cys Asn Ser Lys 80 85 Lys Ala Tyr Phe Leu Tyr Met Tyr Ser Arg Tyr Leu Val Arg Ala Ile 100

Leu Lys Cys His Ser Ala Phe Ser Glu Thr Ser Ile Phe Arg Thr Asn

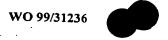
110 115 Gly Lys Val Lys Ser Phe Lys 125 130

<210> 201 <211> 228 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -25..-1

Leu Met Ile Thr Ala Ile Leu Leu Gly Phe Leu Gly Leu Leu Gly 65 60 Ile Ala Gly Leu Arg Cys Thr Asn Ile Gly Gly Leu Glu Leu Ser Arg 80 Lys Ala Lys Leu Ala Ala Thr Ala Gly Ala Pro His Ile Leu Ala Gly 95 Ile Cys Gly Met Val Ala Ile Ser Trp Tyr Ala Phe Asn Ile Thr Arg 105 110 115 Asp Phe Phe Asp Pro Leu Tyr Pro Gly Thr Lys Tyr Glu Leu Gly Pro 130 125 Ala Leu Tyr Leu Gly Trp Ser Ala Ser Leu Ile Ser Ile Leu Gly Gly 145 Leu Cys Leu Cys Ser Ala Cys Cys Cys Gly Ser Asp Glu Asp Pro Ala 155 160 165 Ala Ser Ala Arg Arg Pro Tyr Gln Ala Pro Val Ser Val Met Pro Val 175 Ala Thr Ser Asp Gln Glu Gly Asp Ser Ser Phe Gly Lys Tyr Gly Arg Asn Ala Tyr Val 200

<210> 202 <211> 64 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -47..-1

<210> 203
<211> 146
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -31..-1



<210> 204 <211> 87 <212> PRT <213> Homo sapiens

<210> 205 <211> 40 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -27..-1 <400> 205 Met Arg Thr Leu Phe Gly Ala Val Arg Ala Pro Phe Ser Ser Leu Thr -20 -15 Leu Leu Leu Ile Thr Pro Ser Pro Ser Pro Leu Leu Phe Asp Arg Gly -10 - 5 Leu Ser Leu Arg Ser Ala Met Ser 10

<210> 206 <211> 154 <212> PRT <213> Homo sapiens

<400> 206
Met Gly Ser Leu Ser Gly Leu Arg Leu Ala Ala Gly Ser Cys Phe Arg

10 Leu Cys Glu Arg Asp Val Ser Ser Ser Leu Arg Leu Thr Arg Ser Ser 30 Asp Leu Lys Arg Ile Asn Gly Phe Cys Thr Lys Pro Gln Glu Ser Pro Gly Ala Pro Ser Arg Thr Tyr Asn Arg Val Pro Leu His Lys Pro Thr 55 Asp Trp Gln Lys Lys Ile Leu Ile Trp Ser Gly Arg Phe Lys Lys Glu 70 75 Asp Glu Ile Pro Glu Thr Val Ser Leu Glu Met Leu Asp Ala Ala Lys 90 Asn Lys Met Arg Val Lys Ser Ser Tyr Leu Met Ile Ala Leu Thr Val 100 105 Val Gly Cys Ile Phe Met Val Ile Glu Gly Lys Lys Ala Ala Gln Arg 115 120 His Glu Thr Leu Thr Ser Leu Asn Leu Glu Lys Lys Ala Arg Leu Lys 135 Glu Glu Ala Ala Met Lys Ala Lys Thr Glu 150

<210> 207 <211> 101 <212> PRT <213> Homo sapiens

<400> 207

 Met
 Val
 Cys
 Glu
 Lys
 Lys
 Lys
 Leu
 Gly
 Thr
 Val
 Ile
 Thr
 Pro

 1
 1
 5
 10
 10
 15
 15

 Asp
 Thr
 Thr
 Thr
 Glu
 Ser
 Gly
 Gly
 Arg

 Asp
 Lys
 Asp
 Gly
 Ala
 Leu
 Thr
 Ser
 Lys
 Ala
 Arg
 Phe
 Asp
 Asp
 Asp
 Asp
 Asp
 Asp
 Asp
 Asp
 Arg
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 Arg
 Phe
 Asp
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 Phe
 Asp
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 Phe
 Asp
 Arg
 Arg
 Phe
 Asp
 Arg
 Ile
 Cys
 Lys
 Ser
 Ser
 Ser
 Arg
 Ile
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 Ile
 Cys
 Ala
 Tyr
 Lys
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 Arg
 Ile
 Cys
 Ala
 Tyr
 Lys
 Arg

<210> 208
<211> 456
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -22..-1



			30					35					40		
Glu	Glu	Glu 45	Glu	Glu	Glu	Arg	Lys 50	Lys	Lys	Cys	Pro	Lys 55	Lys	Ala	Ser
	60					65					70	_	_	Lys	
75					80					85				Glu	90
				95					100	_		_		Ala 105	
			110					115					120	Asn	
		125					130			_		135		Trp	_
	140					145					150	=		Thr	
Pro 155	Lys	Pro	Pro	His	Thr 160	Leu	Ser	Arg	Lys	Gln 165	Trp	Arg	Asn	Arg	Gln 170
Lys	Asn	Lys	Arg	Arg 175	Cys	Lys	Asn	Lys	Phe 180	Gln	Pro	Pro	Gln	Val 185	Pro
Asp	Gln	Ala	Pro 190	Ala	Glu	Ala	Pro	Thr 195	Glu	Lys	Thr	Glu	Val 200	Ser	Pro
Val	Pro	Arg 205	Thr	Asp	Ser	His	Gly 210	Ala	Arg	Ala	Gly	Ala 215	Leu	Arg	Ala
Arg	Met 220	Ala	Gln	Arg	Leu	Asp 225	Gly	Ala	Arg	Phe	Arg 230	Tyr	Leu	Asn	Glu
Gln 235	Leu	Tyr	Ser	Gly	Pro 240	Ser	Ser	Ala	Ala	Gln 245	Arg	Leu	Phe	Gln	Glu 250
				255					260	_				Gln 265	
			270					275					280	Leu	
Gln	Arg	Pro 285	Ala	Ser	Leu	Val	Val 290	Ala	Asp	Phe	Gly	Cys 295	Gly	Asp	Cys
Arg	Leu 300	Ala	Ser	Ser	Ile	Arg 305	Asn	Pro	Val	His	Cys 310	Phe	Asp	Leu	Ala
Ser 315	Leu	Asp	Pro	Arg	Val 320	Thr	Val	Cys	Asp	Met 325	Ala	Gln	Val	Pro	Leu 330
Glu	Asp	Glu	Ser	Val 335	Asp	Val	Ala	Val	Phe 340	Cys	Leu	Ser	Leu	Met 345	Gly
Thr	Asn	Ile	Arg 350	Asp	Phe	Leu	Glu	Glu 355	Ala	Asn	Arg	Val	Leu 360	Lys	Pro
Gly	Gly	Leu 365	Leu	Lys	Val	Ala	Glu 370	Val	Ser	Ser	Arg	Phe 375	Glu	Asp	Val
Arg	Thr 380	Phe	Leu	Arg	Ala	Val 385	Thr	Lys	Leu	Gly	Phe 390	Lys	Ile	Val	Ser
Lys 395	Asp	Leu	Thr	Asn	Ser 400	His	Phe	Phe	Leu	Phe 405	Asp	Phe	Gln	Lys	Thr 410
Gly	Pro	Pro	Leu	Val 415	Gly	Pro	Lys	Ala	Gln 420	Leu	Ser	Gly	Leu	Gln 425	
Gln	Pro	Cys	Leu 430		Lys	Arg	Arg								

<210> 209

<211> 98

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -17..-1

<210> 210 <211> 83 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -29..-1

<400> 210 Met Thr Leu Leu Ser Phe Ala Ala Phe Thr Ala Ala Phe Ser Val Leu -20 -25 Pro Cys Tyr Tyr Leu Gly Leu Phe Gln Arg Ala Leu Ala Ser Val Phe -10 -5 Asp Pro Leu Cys Val Cys Ser Arg Val Leu Pro Thr Pro Val Cys Thr 10 Leu Val Ala Thr Gln Ala Glu Lys Ile Leu Glu Asn Gly Pro Cys Pro 25 30 Thr Lys Glu Ala Ala Gln Leu Val Gly Lys Gly Ser Val Ser Ala Arg 45 40 Asn Ala Ser

<210> 211 <211> 229 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -23..-1



50 Gly Lys Thr Leu Val Phe Glu Gln Arg Lys Ser Asp Gly Val His Thr 65 70 Val Glu Thr Glu Val Gly Asp Tyr Met Phe Cys Phe Asp Asn Thr Phe Ser Thr Ile Ser Glu Lys Val Ile Phe Phe Glu Leu Ile Leu Asp Asn 100 95 Met Gly Glu Gln Ala Gln Glu Gln Glu Asp Trp Lys Lys Tyr Ile Thr 115 110 Gly Thr Asp Ile Leu Asp Met Lys Leu Glu Asp Ile Leu Glu Ser Ile 130 125 Ser Ser Ile Lys Ser Arg Leu Ser Lys Ser Gly His Ile Gln Ile Leu 145 Leu Arg Ala Phe Glu Ala Arg Asp Arg Asn Ile Gln Glu Ser Asn Phe 160 Asp Arg Val Asn Phe Trp Ser Met Val Asn Leu Val Val Met Val Val 180 175 Val Ser Ala Ile Gln Val Tyr Met Leu Lys Ser Leu Phe Glu Asp Lys 190 195 Arg Lys Ser Arg Thr 205

<210> 212 <211> 152 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1

<400> 212 Met Ala Gln Leu Gly Ala Val Val Ala Val Ala Ser Ser Phe Phe Cys -15 Ala Ser Leu Phe Ser Ala Val His Lys Ile Glu Glu Gly His Ile Gly Val Tyr Tyr Arg Gly Gly Ala Leu Leu Thr Ser Thr Ser Gly Pro Gly 20 Phe His Leu Met Leu Pro Phe Ile Thr Ser Tyr Lys Ser Val Gln Thr 35 Thr Leu Gln Thr Asp Glu Val Lys Asn Val Pro Cys Gly Thr Ser Gly 50 Gly Val Met Ile Tyr Phe Asp Arg Ile Glu Val Val Asn Phe Leu Val Pro Asn Ala Val His Asp Ile Val Lys Asn Tyr Thr Ala Asp Tyr Asp 85 Lys Ala Leu Ile Phe Asn Lys Ile His His Glu Leu Asn Gln Phe Cys 100 Ser Val His Thr Leu Gln Glu Val Tyr Ile Glu Leu Phe Gly Leu Glu 115 Asn Asp Phe Ser Gln Glu Ser Ser 130

<210> 213 <211> 179 <212> PRT <213> Homo sapiens

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<220>
<221> SIGNAL
<222> -54..-1
<400> 213
Met Ala Ala Ser Glu Ala Ala Val Val Ser Ser Pro Ser Leu Lys Thr
                -50
                                    -45
Asp Thr Ser Pro Val Leu Glu Thr Ala Gly Thr Val Ala Ala Met Ala
Ala Thr Pro Ser Ala Arg Ala Ala Ala Ala Val Ala Ala Ala Ala
                            -15
Arg Thr Gly Ser Glu Ala Arg Val Ser Lys Ala Ala Leu Ala Thr Lys
Leu Leu Ser Leu Ser Gly Val Phe Ala Val His Lys Pro Lys Gly Pro
                                    20
Thr Ser Ala Glu Leu Leu Asn Arg Leu Lys Glu Lys Leu Leu Ala Glu
                                35
Ala Gly Met Pro Ser Pro Glu Trp Thr Lys Arg Lys Lys Gln Thr Leu
                            50
Lys Ile Gly His Gly Gly Thr Leu Asp Ser Ala Ala Arg Gly Val Leu
                        65
Val Val Gly Ile Gly Ser Gly Thr Lys Met Leu Thr Ser Met Leu Ser
                    80
Gly Ser Lys Arg Tyr Thr Ala Ile Gly Glu Leu Gly Lys Ala Thr Asp
                95
                                   100
Thr Leu Asp Ser Thr Gly Lys Val Thr Glu Glu Lys Pro Tyr Gly Met
Asn Leu Ile
       125
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<210> 214 <211> 269 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -92..-1

<400> 214 Met Ile Thr His Val Thr Leu Glu Asp Ala Leu Ser Asn Val Asp Leu -85 -80 Leu Glu Glu Leu Pro Leu Pro Asp Gln Gln Pro Cys Ile Glu Pro Pro -75 -70 -65 Pro Ser Ser Ile Met Tyr Gln Ala Asn Phe Asp Thr Asn Phe Glu Asp -55 -50 Arg Asn Ala Phe Val Thr Gly Ile Ala Arg Tyr Ile Glu Gln Ala Thr -35 Val His Ser Ser Met Asn Glu Met Leu Glu Glu Gly His Glu Tyr Ala -20 Val Met Leu Tyr Thr Trp Arg Ser Cys Ser Arg Ala Ile Pro Gln Val - 5 Lys Cys Asn Glu Gln Pro Asn Arg Val Glu Ile Tyr Glu Lys Thr Val 10 Glu Val Leu Glu Pro Glu Val Thr Lys Leu Met Lys Phe Met Tyr Phe Gln Arg Lys Ala Ile Glu Arg Phe Cys Ser Glu Val Lys Arg Leu Cys His Ala Glu Arg Arg Lys Asp Phe Val Ser Glu Ala Tyr Leu Leu Thr 60

```
Leu Gly Lys Phe Ile Asn Met Phe Ala Val Leu Asp Glu Leu Lys Asn
                      75
Met Lys Cys Ser Val Lys Asn Asp His Ser Ala Tyr Lys Arg Ala Ala
                  90
Gln Phe Leu Arg Lys Met Ala Asp Pro Gln Ser Ile Gln Glu Ser Gln
               105
                                  110
Asn Leu Ser Met Phe Leu Ala Asn His Asn Arg Ile Thr Gln Cys Leu
           120
                              125
His Gln Gln Leu Glu Val Ile Pro Gly Tyr Glu Glu Leu Leu Ala Asp
                          140
Ile Val Asn Ile Cys Val Asp Tyr Tyr Glu Asn Lys Met Tyr Leu Thr
                                160
150 155
Pro Ser Glu Lys His Met Leu Leu Lys Val Lys Leu Pro
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<210> 215 <211> 135 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -22..-1 <400> 215

Met Gln Thr Val Tyr Tyr Gly Ser Leu Gly Leu Trp Leu Ala Leu Val -15 Asp Gly Leu Val Arg Ser Ser Pro Ser Leu Asp Gln Met Phe Asp Ala Glu Ile Leu Gly Phe Ser Thr Pro Pro Gly Arg Leu Ser Met Met Ser 20 Phe Ile Phe Asn Ala Leu Thr Cys Ala Leu Gly Leu Leu Tyr Phe Ile 35 Arg Arg Gly Lys Gln Cys Leu Asp Phe Thr Val Thr Val His Phe Phe 50 His Leu Leu Gly Cys Trp Phe Tyr Ser Ser Arg Phe Pro Ser Ala Leu Thr Trp Trp Leu Val Gln Ala Val Cys Ile Ala Leu Met Ala Val Ile 85 Gly Glu Tyr Leu Cys Met Arg Thr Glu Leu Lys Glu Ile Pro Leu Asn 100 Ser Ala Pro Lys Ser Asn Val 110

<210> 216 <211> 67 <212> PRT <213> Homo sapiens

<220>
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<222> -38..-1

Ala Val Cys Cys Leu Ala Asp Gly Ala Leu Ile Tyr Arg Lys Leu Leu -5 1 5 5 10

Phe Asn Pro Asn Gly Pro Tyr Gln Lys Lys Pro Val His Glu Lys Lys 15 20 25

Glu Val Leu

<210> 217 <211> 125 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -54..-1

<400> 217 Met Ala Asp Glu Glu Leu Glu Ala Leu Arg Arg Gln Arg Leu Ala Glu -50 -45 Leu Gln Ala Lys His Gly Asp Pro Gly Asp Ala Ala Gln Glu Ala -35 -30 Lys His Arg Glu Ala Glu Met Arg Asn Ser Ile Leu Ala Gln Val Leu -20 -15 Asp Gln Ser Ala Arg Ala Arg Leu Ser Asn Leu Ala Leu Val Lys Pro Glu Lys Thr Lys Ala Val Glu Asn Tyr Leu Ile Gln Met Ala Arg Tyr 20 Gly Gln Leu Ser Glu Lys Val Ser Glu Gln Gly Leu Ile Glu Ile Leu 35 Lys Lys Val Ser Gln Gln Thr Glu Lys Thr Thr Thr Val Lys Phe Asn 50 Arg Arg Lys Val Met Asp Ser Asp Glu Asp Asp Asp Tyr

65

<210> 218
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<222> -21..-1
<400> 218

 Met
 Gly
 His
 Arg
 Phe
 Leu
 Arg
 Gly
 Leu
 Leu
 Thr
 Leu
 Leu
 Pro
 Pro
 Pro
 Pro
 Pro
 Pro
 Leu
 Thr
 Arg
 His
 Arg
 Met
 Leu
 Gly
 Pro
 Glu
 Ser
 Val
 Pro

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 Gly
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 Gly
 Ile
 Ile

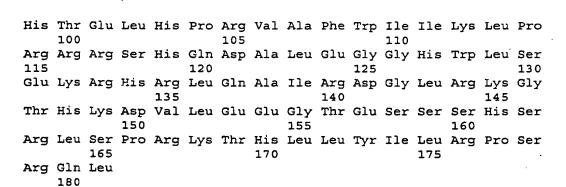


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100
Leu Ser Ser Ala Gly Leu Ile Tyr Leu His Phe Gly His Lys Leu Leu
                            115
                                                120
Ala Gln Leu Leu Gly Thr Ser Glu Glu Asp Ser Met Val Gly Thr Leu
                        130
                                            135
Tyr Asp Lys Met Tyr Glu Asn Phe Val Glu Glu Val Asp Ala Val Asp
                                        150
Asn Gly Ile Ser Gln Trp Ala Glu Gly Glu Pro Arg Tyr Ala Leu Thr
                                    165
Thr Thr Leu Ser Ala Arg Val Ala Arg Leu Asn Pro Thr Trp Asn His
                                180
Pro Asp Gln Asp Thr Glu Ala Gly Phe Lys Arg Ala Met Asp Leu Val
                            195
Gln Glu Glu Phe Leu Gln Arg Leu Asp Phe Tyr Gln His Ser Trp Leu
                        210
Pro Ala Arg Ala Leu Val Glu Glu Ala Leu Ala Gln Arg Phe Gln Val
                    225
                                       230
Asp Pro Ser Gly Glu Ile Val Glu Leu Ala Lys Gly Ala Cys Pro Trp
                240
                                   245
Lys Glu His Leu Tyr His Leu Glu Ser Gly Leu Ser Pro Pro Val Ala
            255
                               260
Ile Phe Phe Val Ile Tyr Thr Asp Gln Ala Gly Gln Trp Arg Ile Gln
        270
                           275
Cys Val Pro Lys Glu Pro His Ser Phe Gln Ser Arg Leu Pro Leu Pro
                       290
                                            295
Glu Pro Trp Arg Gly Leu Arg Asp Glu Ala Leu Asp Gln Val Ser Gly
                   305
                                        310
Ile Pro Gly Cys Ile Phe Val His Ala Ser Gly Phe Ile Gly Gly His
                                   325
Arg Thr Arg Glu Gly Ala Leu Ser Met Ala Arg Ala Thr Leu Ala Gln
                                340
Arg Ser Tyr Leu Pro Gln Ile Ser
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<211> 211
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<400> 219
Met Gly Glu Ala Ser Pro Pro Ala Pro Ala Arg Arg His Leu Leu Val
                   -25
                                        -20
Leu Leu Leu Leu Ser Thr Leu Val Ile Pro Ser Ala Ala Ala Pro
               ~10
                                    -5
Ile His Asp Ala Asp Ala Gln Glu Ser Ser Leu Gly Leu Thr Gly Leu
                           10
Gln_Ser_Leu_Leu Gln-Gly-Phe Ser-Arg Leu-Phe Leu Lys Gly Asn Leu
                       25
                                           30
Leu Arg Gly Ile Asp Ser Leu Phe Ser Ala Pro Met Asp Phe Arg Gly
                   40
                                        45
Leu Pro Gly Asn Tyr His Lys Glu Glu Asn Gln Glu His Gln Leu Gly
               55
                                    60
Asn Asn Thr Leu Ser Ser His Leu Gln Ile Asp Lys Val Pro Arg Met
                               75
Glu Glu Lys Glu Ala Leu Val Pro Ile Gln Lys Ala Thr Asp Ser Phe
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<210> 219

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<210> 220 <211> 154 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -60..-1 <400> 220 Met Gly Ser Lys Cys Cys Lys Gly Gly Pro Asp Glu Asp Ala Val Glu Arg Gln Arg Arg Gln Lys Leu Leu Leu Ala Gln Leu His His Arg Lys -40 -35 ٠. Arg Val Lys Ala Ala Gly Gln Ile Gln Ala Trp Trp Arg Gly Val Leu -25 -20 -15 Val Arg Arg Thr Leu Leu Val Ala Ala Leu Arg Ala Trp Met Ile Gln -10 -5 1 Cys Trp Trp Arg Thr Leu Val Gln Arg Arg Ile Arg Gln Arg Arg Gln 10 15 Ala Leu Leu Arg Val Tyr Val Ile Gln Glu Gln Ala Thr Val Lys Leu 25 30 Gln Ser Cys Ile Arg Met Trp Gln Cys Arg Gln Cys Tyr Arg Gln Met 45

<210> 221 <211> 123 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -42..-1 <400> 221 Met Lys Gly Gly Ala Phe Ser Asn Leu Asn Asp Ser Gln Leu Ser Ala -35 -30 Ser Phe Leu Gln Pro Ser Leu Gln Ala Asn Cys Pro Ala Leu Asp Pro -25 -20

Cys Asn Ala Leu Cys Leu Phe Gln Val Pro Glu Ser Ser Leu Ala Phe 60 Gln Thr Asp Gly Phe Leu Gln Val Gln Tyr Ala Ile Pro Ser Lys Gln

75

Pro Glu Phe His Ile Glu Ile Leu Ser Ile



Ala Val Ser Leu Ser Ala Pro Ala Phe Ala Ser Ala Leu Arg Ser Met Lys Ser Ser Gln Ala Ala Arg Lys Asp Phe Leu Arg Ser Leu Ser 15 Asp Gly Asp Ser Gly Thr Ser Glu His Ile Ser Ala Val Val Thr Ser 30 Pro Arg Ile Ser Cys His Gly Ala Ala Ile Pro Thr Ala Arg Ala Leu 45 Cys Leu Gly Cys Ser Cys Cys Thr Glu Arg Leu Leu Pro Pro Pro 60 Ser Leu Leu Ser Leu Glu Ala Pro Ala Ser Thr 75

<210> 222 <211> 346 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -19..-1

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PCT/IB98/02122 -
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270
                    275
                                        280
Glu Pro Leu His Thr His Trp Pro His Asn Phe Ser Gly Leu Phe Leu
                290
                                    295
Leu Thr Val Gly Ser Ser Ile Leu Thr Ala Phe Leu Leu Ser Gln Leu
                                310
Val Gln Arg Lys Leu Asp Gln Lys Thr Lys
                            325
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<400> 223
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Met Asp Asn Arg Phe Ala Thr Ala Phe Val Ile Ala Cys Val Leu Ser -15 -10 Leu Ile Ser Thr Ile Tyr Met Ala Ala Ser Ile Gly Thr Asp Phe Trp Tyr Glu Tyr Arg Ser Pro Val Gln Glu Asn Ser Ser Asp Leu Asn Lys 20 Ser Ile Trp Asp Glu Phe Ile Ser Asp Glu Ala Asp Glu Lys Thr Tyr 35 Asn Asp Ala Leu Phe Arg Tyr Asn Gly Thr Val Gly Leu Trp Arg Arg Cys Ile Thr Ile Pro Lys Asn Met His Trp Tyr Ser Pro Pro Glu Arg Thr Glu Ser Phe Asp Val Val Thr Lys Cys Val Ser Phe Thr Leu Thr 85 Glu Gln Phe Met Glu Lys Phe Val Asp Pro Gly Asn His Asn Ser Gly 100 105 Ile Asp Leu Leu Arg Thr Tyr Leu Trp Arg Cys Gln Phe Leu Leu Pro 115 120 Phe Val Ser Leu Gly Leu Met Cys Phe Gly Ala Leu Ile Gly Leu Cys 130 135 Ala Cys Ile Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly Ile Leu 145 150 His Leu Leu Ala Val Thr Lys Glu Ser Met Leu Pro Ala Gly Ala Glu 165 Ser Lys His Thr Ala Thr Pro Ala His Ala Cys Val Gln Thr Gly Lys 180

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<210> 224
<211> 184
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -20..-1
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Pro Lys 190

<400> 224



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-20
                     -15
                                         -10
Leu Ile Ser Thr Ile Tyr Met Ala Ala Ser Ile Gly Thr Asp Phe Trp
Tyr Glu Tyr Arg Ser Pro Val Gln Glu Asn Ser Ser Asp Leu Asn Lys
Ser Ile Trp Asp Glu Phe Ile Ser Asp Glu Ala Asp Glu Lys Thr Tyr
Asn Asp Ala Pro Phe Arg Tyr Asn Gly Thr Val Gly Leu Trp Arg Arg
                                        55
Cys Ile Thr Ile Pro Lys Asn Met His Trp Tyr Ser Pro Pro Glu Arg
                                    70
Thr Glu Ser Phe Asp Val Val Thr Lys Cys Val Ser Phe Thr Leu Thr
                                85
Glu Gln Phe Met Glu Lys Phe Val Asp Pro Gly Asn His Asn Ser Gly
                            100
Ile Asp Leu Leu Arg Thr Tyr Leu Trp Arg Cys Gln Phe Leu Leu Pro
                        115
                                            120
Phe Val Ser Leu Gly Leu Met Cys Phe Gly Ala Leu Ile Gly Leu Cys
                    130
                                        135
Ala Cys Ile Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly Ile Leu
                145
                                    150
His Leu Leu Ala Asp Thr Met Leu
            160
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<210> 225
 <211> 227
 <212> PRT
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 <222> -22..-1
<400> 225
Met Gly Trp Thr Met Arg Leu Val Thr Ala Ala Leu Leu Leu Gly Leu
                             -15
Met Met Val Val Thr Gly Asp Glu Asp Glu Asn Ser Pro Cys Ala His
Glu Ala Leu Leu Asp Glu Asp Thr Leu Phe Cys Gln Gly Leu Glu Val
                                     20
Phe Tyr Pro Glu Leu Gly Asn Ile Gly Cys Lys Val Val Pro Asp Cys
                                 35
Asn Asn Tyr Arg Gln Lys Ile Thr Ser Trp Met Glu Pro Ile Val Lys
                            50
Phe Pro Gly Ala Val Asp Gly Ala Thr Tyr Ile Leu Val Met Val Asp
                        65
Pro Asp Ala Pro Ser Arg Ala Glu Pro Arg Gln Arg Phe Trp Arg His
                    80
                                        85
Trp Leu Val Thr Asp Ile Lys Gly Ala Asp Leu Lys Lys Gly Lys Ile
                95
                                    100
Gln_Gly_Gln-Glu-Leu-Ser-Ala Tyr-Gln Ala Pro Ser Pro Pro Ala His
            110
                                115
Ser Gly Phe His Arg Tyr Gln Phe Phe Val Tyr Leu Gln Glu Gly Lys
                            130
Val Ile Ser Leu Leu Pro Lys Glu Asn Lys Thr Arg Gly Ser Trp Lys
                        145
Met Asp Arg Phe Leu Asn Arg Phe His Leu Gly Glu Pro Glu Ala Ser
                    160
                                        165
Thr Gln Phe Met Thr Gln Asn Tyr Gln Asp Ser Pro Thr Leu Gln Ala
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PCT/IB98/02122 -
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Pro Arg Glu Arg Ala Ser Glu Pro Lys His Lys Asn Gln Ala Glu Ile
190 195 200

Ala Ala Cys
205

<210> 226 <211> 74 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -41..-1

Thr Ala Phe Phe Leu Leu Asp Ile Ile Leu 25 30

<210> 227 <211> 73 <212> PRT <213> Homo sapiens

<210> 228
<211> 82
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 228

Met Lys Arg Leu Leu Pro Ala Thr Ser Leu Ala Gly Pro Val Leu Ser
-15 -10 -5
Thr Leu Ile Ala Pro Thr Pro Met Leu Phe Cys Glu Asp Lys Ser Trp



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<210> 229
<211> 119
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -56..-1
<400> 229
Met Ala Glu Pro Ser Ala Ala Thr Gln Ser His Ser Ile Ser Ser Ser
                        -50
Ser Phe Gly Ala Glu Pro Ser Ala Pro Gly Gly Gly Ser Pro Gly
                    -35
Ala Cys Pro Ala Leu Gly Thr Lys Ser Cys Ser Ser Ser Cys Ala Asp
                                    -15
Ser Phe Val Ser Ser Ser Ser Gln Pro Val Ser Leu Phe Ser Thr
Ser Gln Glu Gly Leu Ser Ser Leu Cys Ser Asp Glu Pro Ser Ser Glu
Ile Met Thr Ser Ser Phe Leu Ser Ser Glu Ile His Asn Thr Gly
                                       35
Leu Thr Ile Leu His Gly Glu Lys Ser His Val Leu Gly Ser Gln Pro
                                   50
Ile Leu Ala Lys Lys Lys
           60
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<210> 231
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<212> PRT
<213> Homo sapiens
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<210> 230 <211> 54

<220> <221> SIGNAL <222> -14..-1

<400> 231

Met Leu Thr Leu Leu Gly Leu Ser Phe Ile Leu Ala Gly Leu Ile Val -10 - 5 Gly Gly Ala Cys Ile Tyr Lys Tyr Phe Met Pro Lys Ser Thr Ile Tyr 10 Arg Gly Glu Met Cys Phe Phe Asp Ser Glu Asp Pro Ala Asn Ser Leu 25 Arg Gly Glu Pro Asn Phe Leu Pro Val Thr Glu Glu Ala Asp Ile 45 Arg Glu Asp Asp Asn Ile Ala Ile Ile Asp Val Pro Val Pro Ser Phe 60 Ser Asp Ser Asp Pro Ala Ala Ile Ile His Asp Phe Glu Lys Gly Met 75 Thr Ala Tyr Leu Asp Leu Leu Leu Gly Ile Cys Tyr Leu Met Pro Leu 90 Asn Thr Ser Ile Val Met Pro Pro Lys Asn Leu Val Glu Leu Phe Gly 105 110 Lys Leu Ala Ser Gly Arg Tyr Leu Pro Gln Thr Tyr Val Val Arg Glu 120 125 Asp Leu Val Ala Val Glu Glu Ile Arg Asp Val Ser Asn Leu Gly Ile 135 140 Phe Ile Tyr Gln Leu Cys Asn Asn Arg Lys Ser Phe Arg Leu Arg Arg 150 155 Arg Asp Leu Leu Gly Phe Asn Lys Arg Ala Ile Asp Lys Cys Trp 170 175

Lys Ile Arg His Phe Pro Asn Glu Phe Ile Val Glu Thr Lys Ile Cys

190

<210> 232 <211> 108 <212> PRT

<213> Homo sapiens

<400> 232

Gln Glu 195

Met Gly Cys Val Phe Gln Ser Thr Glu Asp Lys Cys Ile Phe Lys Ile 10 15 Asp Trp Thr Leu Ser Pro Gly Glu His Ala Lys Asp Glu Tyr Val Leu 30 Tyr Tyr Tyr Ser Asn Leu Ser Val Pro Ile Gly Arg Phe Gln Asn Arg 40 Val His Leu Met Gly Asp Ile Leu Cys Asn Asp Gly Ser Leu Leu Leu 55 Gln Asp Val Gln Glu Ala Asp Gln Gly Thr Tyr Ile Cys Glu Ile Arg Leu Lys Gly Glu Ser Gln Val Phe Lys Lys Ala Val Val Leu His Val 90 Leu Pro Glu Glu Pro Lys Gly Thr Gln Met Leu Thr

<210> 233 <211> 43

<210> 234

<210> 235

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-161-
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<211> 307 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -13..-1 <400> 235 Met Leu Ala Val Ser Leu Thr Val Pro Leu Gly Ala Met Met Leu -10 - 5 Leu Glu Ser Pro Ile Asp Pro Gln Pro Leu Ser Phe Lys Glu Pro Pro 10 Leu Leu Gly Val Leu His Pro Asn Thr Lys Leu Arg Gln Ala Glu 25 30 Arg Leu Phe Glu Asn Gln Leu Val Gly Pro Glu Ser Ile Ala His Ile 40 Gly Asp Val Met Phe Thr Gly Thr Ala Asp Gly Arg Val Val Lys Leu Glu Asn Gly Glu Ile Glu Thr Ile Ala-Arg Phe Gly Ser Gly Pro Cys Lys Thr Arg Asp Asp Glu Pro Val Cys Gly Arg Pro Leu Gly Ile Arg 90 Ala Gly Pro Asn Gly Thr Leu Phe Val Ala Asp Ala Cys Lys Gly Leu 105 110 Phe Glu Val Asn Pro Trp Lys Arg Glu Val Lys Leu Leu Ser Ser 125 Glu Thr Pro Ile Glu Gly Lys Asn Met Ser Phe Val Asn Asp Leu Thr

Val Ser Gln Asp Gly Arg Lys Ile Tyr Phe Thr Asp Ser Ser Ser Lys 155 160 Trp Gln Arg Arg Asp Tyr Leu Leu Leu Val Met Glu Gly Thr Asp Asp 170 175 Gly Arg Leu Leu Glu Tyr Asp Thr Val Thr Arg Glu Val Lys Val Leu 185 190 Leu Asp Gln Leu Arg Phe Pro Asn Gly Val Gln Leu Ser Pro Ala Glu 205 Asp Phe Val Leu Val Ala Glu Thr Thr Met Ala Arg Ile Arg Arg Val 215 220 Tyr Val Ser Gly Leu Met Lys Gly Gly Ala Asp Leu Phe Val Glu Asn 235 Met Pro Gly Phe Pro Asp Asn Ile Arg Pro Ser Ser Ser Gly Gly Tyr 250 255 Trp Val Gly Met Ser Thr Ile Arg Pro Asn Pro Gly Phe Ser Met Leu 265 270 Asp Phe Leu Ser Glu Arg Pro Trp Ile Lys Arg Met Ile Phe Lys Ala Lys Lys Lys

<210> 236 <211> 106 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -32..-1

<210> 237 <211> 42 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -19..-1 <400> 237

Met Asp Leu Arg Gln Phe Leu Met Cys Leu Ser Leu Cys Thr Ala Phe -15 -10 -5 Ala Leu Ser Lys Pro Thr Glu Lys Lys Asp Arg Val His His Glu Pro



1 5
Gln Leu Ser Asp Lys Val His Asn Asp Ile
15 20

<210> 238 <211> 117 <212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -20..-1

<400> 238

Met Asp Asn Arg Phe Ala Thr Ala Phe Val Ile Ala Cys Val Leu Ser
-20 -15 -10 -5

Leu Ile Ser Thr Ile Tyr Met Ala Ala Ser Ile Gly Thr Asp Phe Trp

Tyr Glu Tyr Arg Ser Pro Val Gln Glu Asn Ser Ser Asp Leu Asn Lys
15 20 25

Ser Ile Trp Asp Glu Phe Ile Ser Asp Glu Ala Asp Glu Lys Thr Tyr 30 35 40

Asn Asp Ala Leu Phe Arg Tyr Asn Gly Thr Val Gly Leu Trp Gly Arg
45
50
60

Cys Ile Thr Ile Pro Lys Asn Met His Trp Tyr Ser Pro Pro Glu Arg

Thr Gly Ile Ser Leu Ile Leu Thr Ser Val Phe Phe Thr Trp Leu Ile 80 85 90

Ile Asp Lys Thr Thr 95

<210> 239

<211> 178

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -37..-1

<400> 239

Met Glu Arg Gln Ser Arg Val Met Ser Glu Lys Asp Glu Tyr Gln Phe
-35
-30
-25

Gln His Xaa Xaa Ala Xaa Xaa Leu Leu Val Phe Asn Phe Leu Leu Ile
-20
-15
-10

Leu Thr Ile Leu Thr Ile Trp Leu Phe Lys Asn His Arg Phe Arg Phe

-5 1 5 10 Leu His Glu Thr Gly Gly Ala Met Val Tyr Gly Leu Ile Met Gly Leu

15 20 25 Ille Ser Arg Tyr Ala Thr Ala Pro Thr Asp Ile Glu Ser Gly Thr Val

Cys Asp Cys Val Lys Leu Thr Phe Ser Pro Pro Thr Leu Leu Val Asn 45 50 55

Val Thr Asp Gln Val Tyr Glu Tyr Lys Tyr Lys Arg Glu Ile Ser Gln 60 70 75

His Asn Ile Asn Pro His Gln Gly Asn Ala Ile Leu Glu Lys Met Thr

Phe Asp Pro Glu Ile Phe Phe Asn Val Leu Pro Pro Ile Ile Phe

```
95 100 105

His Ala Gly Tyr Ser Leu Lys Lys Arg His Phe Phe Gln Asn Leu Gly
110 115 120

Ser Ile Leu Thr Tyr Ala Phe Leu Gly Thr Ala Ile Ser Cys Ile Val
125 130 135

Ile Gly
140
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<210> 240 <211> 126 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -27..-1 <400> 240

Met Gln Phe Val Asn Val Gly Tyr Phe Leu Ile Ala Ala Gly Val Val -20 Val Leu Ala Leu Gly Phe Leu Gly Cys Tyr Gly Ala Lys Thr Glu Ser Met Cys Ala Leu Val Thr Phe Phe Phe Ile Leu Leu Ile Phe Ile 15 Ala Glu Val Ala Ala Val Val Ala Leu Val Tyr Thr Thr Met Ala Glu His Phe Leu Thr Leu Leu Val Val Pro Ala Ile Lys Lys Asp Tyr 45 Gly Ser Gln Glu Asp Phe Thr Gln Val Trp Asn Thr Thr Met Lys Gly 60 65 Leu Lys Cys Arg Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp Ser Pro 75 80 Tyr Phe Lys Met His Lys Pro Val Thr Met Lys Lys Lys 90

<210> 241 <211> 174 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -115..-1 <400> 241

Met Arg Trp Ser Cys Glu His Leu Val Met Val Trp Ile Asn Ala Phe -110 -105 Val Met Leu Thr Thr Gln Leu Leu Pro Ser Lys Tyr Cys Asp Leu Leu -95 -90 His Lys Ser Ala Ala His Leu Gly Lys Trp Gln Lys Leu Glu His Gly -80 -75 Ser Tyr Ser Asn Ala Pro Gln His Ile Trp Ser Glu Asn Thr Ile Trp -60 -55 Pro Gln Gly Val Leu Val Arg His Ser Arg Cys Leu Tyr Arg Ala Met -45 Gly Pro Tyr Asn Val Ala Val Pro Ser Asp Val Ser His Ala Arg Phe -35 -30 -25 Tyr Phe Leu Phe His Arg Pro Leu Arg Leu Leu Asn Leu Leu Ile Leu



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<222> 864..869
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<222> 882..893
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                   Met Pro Ser Val Asn Ser Ala Gly Leu Cys Val
                   -20
                                        -15
ttg cag ttg aca acg gca gtr acc agt gcc ttt tta cta gca aaa gtg
                                                                       98
Leu Gln Leu Thr Thr Ala Val Thr Ser Ala Phe Leu Leu Ala Lys Val
                -5
aat cct ttc gaa rct ttt ctc tca agg ggc ttt tgg cta tgt gcc
                                                                      146
Asn Pro Phe Glu Xaa Phe Leu Ser Arg Gly Phe Trp Leu Cys Ala Ala
                            15
cat cat ttc att cat cct tgc ctg gat tgagacgtgt tcctgattca
                                                                      193
His His Phe Ile His Pro Cys Leu Asp
                        30
aagtgttacc tcaagaagca gaagaagaaa acagactcct gatagttcag gatgcttcag
                                                                      253
agagggcage acttatacet ggtggtettt etgatggtea gttttattee ecteetgaat
                                                                      313
ccgaagcagg atctgaagaa gctgaagaaa aacaggacag tgagaaacca cttttagaac
                                                                      373
tatgagtact acttttgtta aatgtgaaaa accctcacag aaagtcatcg aggcaaaaag
                                                                      433
aggcaggcag tggagtctcc ctgtcgacag taaagttgaa atggtgacgt ccactgctgg
                                                                      493
ctttattgaa cagctaataa agatttattt attgtaatac ctcacagacg ttgtaccata
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ttcagtgaga ctgagcctga tgtgttaaca aataggtgaa gaaagtcttg tgctgtattc
                                                                      673
ctaatcaaaa gacttaatat attgaagtaa cactttttta gtaagcaaga taccttttta
                                                                      733
tttcaattca cagaatggaa tttttttgtt tcatgtctca gatttatttt gtatttcttt
                                                                      793
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	0 > 2															
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Glu	Arg	Gly	gcc Ala	Glu 10	Arg	Arg	Asp	Thr	Ala 15	Pro	Ser	Gly	Val	Ser 20	Arg	148
ttc Phe	tgc Cys	cct Pro	cca Pro 25	aga Arg	aag Lys	tct Ser	tgc Cys	cat His 30	gat Asp	tgg Trp	ata Ile	gga Gly	ccc Pro 35	cca Pro	gat Asp	196
aaa Lys	tat Tyr	tca Ser 40	aac Asn	ctt Leu	cga Arg	cct Pro	gtt Val 45	cac His	ttt Phe	tac Tyr	ata Ile	cct Pro 50	gaa Glu	aat Asn	gaa Glu	244
Ser	Pro 55	Leu	gaa Glu	Gln	Lys	Leu 60	Arg	Lys	Leu	Arg	Gln 65	Glu	Thr	Gln	Glu	292
Trp 70	Asn	Gln	cag Gln	Phe	Trp 75	Ala	Asn	Gln	Asn	Leu 80	Thr	Phe	Ser	Lys	Glu 85	340
ьуs	GIu	Glu	ttt Phe	Ile 90	His	Ser	Arg	Leu	Lys 95	Thr	Lys	Gly	Leu	Gly 100	Leu	388
Arg	Tnr	Glu	tca Ser 105	Gly	Gln	Lys	Ala	Thr 110	Leu	Asn	Ala	Glu	Glu 115	Met	Ala	436
Asp	Phe	Tyr 120	aag Lys	Glu	Phe	Leu	Ser 125	Lys	Asn	Phe	Gln	Lys 130	His	Met	Tyr	484
ryr	Asn 135	Arg	gat Asp	Trp	Tyr	Lys 140	Arg	Asn	Phe	Ala	Ile 145	Thr	Phe	Phe	Met	532
31y 150	Lys	Val	gcc Ala	Leu	Glu 155	Arg	Ile	Trp	Asn	Lys 160	Leu	Lys	Gln	Lys	Gln 165	580
aag Lys	aag Lys	agg Arg	agc Ser	aac Asn 170	tagg	gagto	ca d	ctctc	gacco		caga	gtcc	agg	gttt	ccac	635
19 <b>5</b> 0	aagca	ara (	tggaç cttc	gctcc	t tt 9 99	caca	gggg atgg	g cto	tgag gttt	gaaa :ggg	aact ggca	ggag	ct g	gatet gteet	caaga ggggc	695 755



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ctg cag gca gcc ctg ctc tgc gtc aac gcc atc gca gtg ctg cac gag Leu Gln Ala Ala Leu Leu Cys Val Asn Ala Ile Ala Val Leu His Glu -5 10	160
Glu Arg Phe Leu Lys Asn Ile Gly Trp Gly Thr Asp Gln Gly Ile Gly  15	208
gga ttt gga gaa gag ccg gga att aaa tca sag sta atg avs ctt att Gly Phe Gly Glu Glu Pro Gly Ile Lys Ser Xaa Xaa Met Xaa Leu Ile 30 35 40	256
cga tct gta aga acc gtg atg aga gtg cca ttg ata ata gta aac tca Arg Ser Val Arg Thr Val Met Arg Val Pro Leu Ile Ile Val Asn Ser 45 50 55	304
att gca att gtg tta ctt tta tta ttt gga tgaatwtcat tggagaaaat  Ile Ala Ile Val Leu Leu Leu Phe Gly  60  65	354
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Solit   Soli	-10	AIA	Met	νa1	Thr	Arg -5	Pro	Ala	Ser	Ala	Ala 1	Pro	Met	Gly	Gly	Pro	101
Second   S	GIU	ьeu	Ala	10	His	Glu	Glu	Leu	Thr	Leu	Leu	Phe	His	Gly	Thr	Leu	149
Ato	GIII	Leu	25	GIN	ATA	Leu	Asn	GIA	Val	Tyr	Arg	Thr	Thr	Glu	Gly	Arg	197
Ser	Deu	40	ьys	Ala	Arg	Asn	Ser 45	Leu	Gly	Leu	Tyr	Gly 50	Arg	Thr	Ile	Glu	245
Cag   Ga   rag   Ga   cac   gat	55	Deu	GIÀ	GIN	GIU	60	ser	Arg	Gly	Arg	Asp	Ala	Ala	Gln	Glu	Leu	293
Ala Ala Thr Ala Glu Val Leu Gly Glu Val Ala Gln Ala Gln 90  aag gtg cta cgg gac agc gtg cag cgg cta daa ktc cag ctg arg asc Lys Val Leu Arg Asp Ser Val Gln Arg Leu Xaa Xaa Gln Leu Xaa Xaa 105  gcc tgg ctg ggc cct gcc tac cga aaa ttt gar gtc tta aag gcy ccc Ala Trp Leu Gly Pro Ala Tyr Arg Lys Phe Glu Val Leu Lys Ala Pro 120  cck gam aar car aac cac atc cta tgg gcc ctc aca ggc cac gtg cak Pro Xaa Lys Gln Asn His Ile Leu Trp Ala Leu Thr Gly His Val Xaa 135  140  145  150  cgg car arg cgg gar atg gtg gca cag cag cwt ckg ctg cna car atc Arg Gln Xaa Arg Glu Met Val Ala Gln Gln Xaa Xaa Leu Xaa Gln Ile 155  160  cag gar aaa ctc cac aca gcg gcg ctc cca gcc tgaatctgcc tggatggaac Gln Glu Lys Leu His Thr Ala Ala Leu Pro Ala 170  tgaggaccaa tcatgctgca aggaacactt ccacgccccg tgaggccct gtgcagggag gagctgctg ttcactggga tcagccaggg cgccgggccc cacttctgag cacagagcar agaacagacgc aggcgggac aaaggcagag gatgtagccc cacttctgag gggtggagga 814 agaaaaaaaaaa	Arg	AIA	ser	Leu	ьеи 75	GIu	Thr	Gin	Met	Glu 80	Glu	Asp	Ile	Leu	Xaa 85	Leu	341
Second   S	GIII	AIA	naa	90	Thr	Ala	GIu	Val	Leu 95	Gly	Glu	Val	Ala	Gln	Ala	Gln	389
cck gam aar car aac cac atc cta tgg gcc ctc aca ggc cac gtg cak 533 Pro Xaa Lys Gln Asn His Ile Leu Trp Ala Leu Thr Gly His Val Xaa 135	nys	vai	105	Arg	Asp	Ser	Val	Gln 110	Arg	Leu	Xaa	Xaa	Gln	Leu	Xaa	Xaa	437
135 140 145 150 150 150 150 150 165 165 165 165 170 175 175 175 175 175 175 175 175 175 175	nia	120	neu	GIY	Pro	Ala	Tyr 125	Arg	Lys	Phe	Glu	Val	Leu	Lys	Ala	Pro	485
Arg Gin Maa Arg Giu Met Val Ala Gin Gin Xaa Xaa Leu Xaa Gin Ile  155 160 165  Cag gar aaa ctc cac aca gcg gcg ctc cca gcc tgaatctgcc tggatggaac 634  Gin Giu Lys Leu His Thr Ala Ala Leu Pro Ala  170 175  tgaggaccaa tcatgctgca aggaacactt ccacgccccg tgaggcccct gtgcagggag 694  gagctgcctg ttcactggga tcagccaggg cgccgggccc cacttctgag cacagagcar 754  agacagacgc aggcggggac aaaggcagag gatgtagccc cattggggag gggtggagga 814  aggacatgta ccctttcatr mctacacacc cctcattaaa gcavagtcgt ggcatctcaa 874	135	Add	пув	GIN	Asn	H1S	lle	Leu	Trp	Ala	Leu 145	Thr	Gly	His	Val	Xaa 150	533
170 175  tgaggaccaa tcatgctgca aggaacactt ccacgccccg tgaggcccct gtgcagggag 694 gagctgcctg ttcactggga tcagccaggg cgccgggccc cacttctgag cacagagcar 754 agacagacgc aggcggggac aaaggcagag gatgtagccc cattggggag gggtggagga 814 aggacatgta ccctttcatr mctacacacc cctcattaaa gcavagtcgt ggcatctcaa 874	Arg	GIII	Aaa	Arg	G1u 155	Met	Val	Ala	Gln	Gln 160	Xaa	Xaa	Leu	Xaa	Gln	Ile	581
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aaaaaaaaaa	agac	agac	yc a	ggcg	ggga	c aa	aggc	aqaq	qat	ataa	CCC	catt	aaaa	20 0	aata	~~~~	814
	-35~	cacg	ca c		LCat	r mc	caca	cacc	cct	catt	aaa	gcav	agtc	gt g	gcat	ctcaa	

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						-	JJJ-	- 5-	Me	t De	n La	re T.e	.y a.a	ig as	s Val	114
									-5		ער עי	2 DC	u by	-		
cto	age	aaa	Cac	gac	200	~~~	~~~			<b>3</b>				- 5	0	
Leu	agc Ser	GJV	Gla	yez gac	Th.	gag	gac	cgg	agc	aac	ctg	tcc	gag	gtt	gtt	162
	Ser	<b>-</b>	-45	Asp	1111	Giu	Asp	Arg	Ser	GTA	Leu	Ser	Glu	. Val	Val	
gag	ac-	+ =+						-40					-35			
Glu	gca Ala	60.	Cca	tta	agc	tgg	agt	acc	agg	ata	aaa	ggc	ttc	att	gcg	210
Gru	Ala	261	SET	Leu	ser	Trp	ser	Thr	Arg	Ile	Lys	Gly	Phe	Ile	Ala	
		-30					~25					-20				
rgt.	ttt Phe	gct	ata	gga	att	ctc	tgc	tca	ctg	ctg	ggt	act	gtt	ctq	cta	258
Cys		Ala	Ile	Gly	Ile	Leu	Cys	Ser	Leu	Leu	Gly	Thr	Val	Leu	Leu	
						- TO					-5					
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1	Val	Pro	Arg	Lys	Gly	Leu	His	Leu	Phe	Āla	Val	Phe	Tyr	Thr	Dhe	500
1				5					10				- 7	15	FIIC	
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Gly	Asn	Ile	Ala	Ser	Ile	Glv	Ser	Thr	Tle	Dhe	Ton	Mot	gga	Des	gra	354
			20			7	001	25	116	FILE	ъeи	Met		Pro	Val	
aaa	cag	cta	aac	cga	ato	+++	<b>G</b> = <b>G</b>	23			1		30			
Lys	Gln	Leu	Lvs	Ara	Met	Dhe	949	Dwa	act mb	cgt	ttg	att	gca	act	atc	402
•		35	-, -	9	ric c	FIIC	40	PIO	Inr	Arg	Leu	Ile	Ala	Thr	Ile	
ato	ata		tta	+ ~+	+++		40					45				
Met	gtg Val	Len	Lou	Cur	Dha	gca 33-	-	acc	ctg	tgt	tct	gcc	ttt	t <b>g</b> g	tgg	450
	Val 50	nea	пец	Cys	Pne	Ala	Leu	Thr	Leu	Cys	Ser	Ala	Phe	Trp	Trp	
	J (					55					60					
Hic	aac Aen	aag	99a	CEE	gca	ctt	atc	ttc	tgc	att	ttg	cag	tct	ttg	gca	498
65	Asn	гàг	GIA	Leu	Ата	Leu	Ile	Phe	Cys	Ile	Leu	Gln	Ser	Leu	Ala	
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ьeu	Thr	Trp	Tyr	Ser	Leu	Ser	Phe	Ile	Pro	Phe	Āla	Arg	Asp	Āla	Val	
				85					90					0=		
aaa	aad	tgt	ttt	gcc	gtg	tgt	ctt	gca	taat	tcat	aa c	cagt	ttta	+		593
<b>-</b> 2 y 5	Add	Cys	Pne .	Ala	vaı	Cys	Leu	Ala				5-				333
			100_					105 -								
gaag	cttt	gg a	aggc	acta	t ga	acaq	aaqc	taa	taaa	cac	++++	atwa	a+ >		cgaaa	650
cctc	tgtc	tt a	caga	catq	t ac	cttt	tatc	tta	cade	225	atat	gcwa	te a		cgaaa cgaac	653
attt	gagg	gt t	actt	ttaa	a ao	caac	aata	Cat	90	~~ .	2-7-	2266	to c	yatt att	cgaac cacag	713
gatg	agaa	gt a	ggtt	ctat	a to	ttat	agag	tac	22+~	++c		aalg	cc a	gtag	cacag cctct	773
ctgg	atgt	tq t	CCCA	ctaa	a tt	CCCA	בייננ בבייל	tac	2226		ucca	igta 	CC E	gttt	cctct aaaaa	833
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                                                                      109
               Met Lys Ala Leu Cys Leu Leu Leu Pro Val Leu
ggg ctg ttg gtg tct agc aag acc ctg tgc tcc atg gaa gaa gcc atc
                                                                      157
Gly Leu Leu Val Ser Ser Lys Thr Leu Cys Ser Met Glu Glu Ala Ile
                                        5
aat gag agg atc cag gag gtc gcc ggc tcc cta ata ttt agg gca ata
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Asn Glu Arg Ile Gln Glu Val Ala Gly Ser Leu Ile Phe Arg Ala Ile
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age age att gge ega ggg age gag age gte ace tee agg ggg gae etg
                                                                      253
Ser Ser Ile Gly Arg Gly Ser Glu Ser Val Thr Ser Arg Gly Asp Leu
                                35
get act tge eec ega gge tte gee gte ace gge tge act tgt gge tee
                                                                      301
Ala Thr Cys Pro Arg Gly Phe Ala Val Thr Gly Cys Thr Cys Gly Ser
        45
gcc tgt ggc tcg tgg gat gtg cgc gcc gag acc aca tgt cac tgc cag
                                                                      349
Ala Cys Gly Ser Trp Asp Val Arg Ala Glu Thr Thr Cys His Cys Gln
                        65
tgc gcg ggc atg gac tgg acc gga gcg cgc tgc tgt cgt gtg cag ccc
                                                                     397
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Cys Ala Gly Met Asp Trp Thr Gly Ala Arg Cys Cys Arg Val Gln Pro

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85

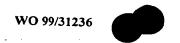
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Ser Arg Gln Leu Arg Ser Leu Ser Cys Leu Cys Pro Ala Leu Phe Pro	104												
-10 _E													
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Gly Thr Ser Ser Phe Ile Val Ala Leu Ser Ser Pro Ala Asp Leu Tyr	132												
310													
atc cct cav agg cas cga tct gat gaa ttg gtt ttt gaa tcc car aaa	200												
Ile Pro Xaa Arg Xaa Arg Ser Asp Glu Leu Val Phe Glu Ser Gln Lys	200												
15													
25													
ggg tot gcc atg gag ttg gca gtc atc acg gta rat ggc gta	242												
Gly Ser Ala Met Glu Leu Ala Val Ile Thr Val Xaa Gly Val													
30													
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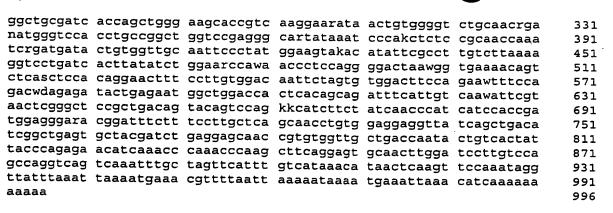
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<222> 986..996

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ttc ctg wgt cta atg acc ctg aca acc cat gtg Phe Leu Xaa Leu Met Thr Leu Thr Thr His Val -10 -5	-15 t cac tca agt gcc aag 164 l His Ser Ser Ala Lys
cca aat gaa caa ccc tgg ttg ttg aac tagcac Pro Asn Glu Gln Pro Trp Leu Leu Asn 5 10	
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-	•
gto cat dad aga sch cha kda soc too oke ook	
gtc cat dac aga ccb cba kda ccc tca akc cat ctg gtt ttc atg agg Val His Xaa Arg Pro Xaa Xaa Pro Ser Xaa His Leu Val Phe Met Arg	440
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145 150 150 171 Ala Gly lie lie Ala Gly Glu	
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Ser Ile Arg Asn Arg Ser	632
160 165	
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ctt ctc ccg ttg ctg ctg ctc tgc ggc cct tcc cag gat caa tgc	101
Leu Leu Pro Leu Leu Leu Leu Cys Gly Pro Ser Gln Asp Gln Cys -15	
-10 -5	
Arg Pro Val Leu Gla Arg Lou Lou Gla Grand age coa gge ttg aca tgg age	149
Arg Pro Val Leu Gln Asn Leu Leu Gln Ser Pro Gly Leu Thr Trp Ser	
10	
ttg gaa gtg ccc act ggg aga gaa gga aag gaa ggt ggg gat cgg gga	197
out val in Gly Arg Glu Gly Lys Glu Gly Gly Asp Arg Gly	
25	
cca ggg cta akt ggg gcc act cca gcc agg agc cct cag ggc aag gag	245
20 And Gly Ald inf Pro Ala Arg Ser Pro Gln Gly Lys Glu	
35 40 45 45 45 45 45 45 45 45 45 45 45 45 45	

50

40

55

atg ggg aga caa agg acc aga aag gtg aag ggc cct gct tgg akt cac Met Gly Arg Gln Arg Thr Arg Lys Val Lys Gly Pro Ala Trp Xaa His

45

60

293

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	cca Pro												389
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	gct Ala												485
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<221> sig\_peptide

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seq VAFMLTLPILVCK/VQ

<221> polyA\_site <222> 1104..1114

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ьeu	Pne	GTA	Ile	Leu	Phe	Ser	Ile	Cys	Phe	Ser	Cys	Leu	Leu	Ala	His		•
45 705	~+~	~~+			50					55					60		
212	Val	Sor	Tou	acc	aag	CTC	gtc	cgg	<b>a</b> aa	agg	aaa	gcc	cct	ttc	cct		501
n1a	Val	Ser	пеп	65	гÀг	ren	vai	Arg	70	Arg	Lys	Ala	Pro	Phe 75	Pro		
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Val	Gly	Asp	Ser	Gly	Ser	Gly	Arg	Gly	Leu	Gln	Pro	Ser	Pro	Gly	Cys		
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tat	cgc	tat	tgaa	tata	tt g	tcct	gaco	a tg	aata	ggad	caa	cgtc	aat				598
ıyr_	Arg	1yr 95															
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stac	tett	ct t	rato	cccs	+ ~		act	aat	gaaa	act	ttgt	cctc	ct c	jctca	cctac		658
	acta	779 9	gacy	9090	L ya		CCEC	weg	TCCT	CCT	tcac	cttc	tg t	ggtk	ccttc		718
	+~~	94 6	vaya	catg	9 99	ccca	catc	tac	ctca	sga	tgct	cskc	tc c	attg	ccatc		778
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1 CCII	LCar	1	cgcc	ttgg	s tr	csaa	tggc	tgg	gtgt	tcc	tgtt	ggct	ta t	gtta	gtccc		898
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gta	aacc	tc a	actc	gtga	a ga	agag	ctat	ggt	gtgg	rga	acaq	agcc	ta s	kctc	aagag	10	018
jaaa	tcac	tc a	aggt	tttg	a ag	agac	aggg	gac	acgc	tct	atgc	cccc	ta t	tcca	cacat	10	78
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cedcede	cgt ttcc	tgattg	gttgt	gggtg	g gc	tacc	tctt	cati	tcta	att	aacc	ctagt	120
gagcaag	atg ctg	agc a	ıg ggt	ctg	aag	cgg	aaa	cgg	gag	gag	gag	gag	169
	Met Leu	Ser Ly	s Gly	Leu	Lys	Arq	Lys	Ara	Glu	Glu	Glu	Glu	
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gag aag	gaa cct	ctg go	a gtc	gac	tcc	tgg	tgg	cta	qat	-cct	aac	cac	217 -
Glu Lys	Glu Pro	Leu Al	a Val	Asp	Ser	Trp	Tro	Leu	Asp	Pro	Glv	His	
	-15			-10		-			-5			****	
gca gcg	gtg gca	cag go	a ccc	ccg	gcc	gtg	gcc	tct	agc	tcc	ctc	ttt	265
Ala Ala	Val Ala	Gln Al	a Pro	Pro	Ala	Val	Āla	Ser	Ser	Ser	Len	Phe	-02
1		5					10					15	
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Asp Leu	Ser Val	Leu Lv	s Leu	His	His	Ser	T.011	Gla	Van	Cox	vas	Door	313
_		20		*****	1113	25	Den	GIII	Aaa	ser		Pro	
gac ctg	CGG										30		
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Asp	Leu	Arg	His 35	Leu	Val	Leu	Val	Xaa 40	Asn	Thr	Leu	Arg	Arg 45	Ile	Gln	
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			ant Xaa													457
			tcc Ser													505
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		Ile	999 Gly 115													601
			act Thr													649
gag Glu	gat Asp 145	att Ile	gac Asp	acc Thr	tct Ser	atg Met 150	tat Tyr	gac Asp	aat Asn	gaa Glu	ctt Leu 155	tgg Trp	gca Ala	cca Pro	gcc Ala	697
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			ctg Leu													793
			cag Gln 195													835
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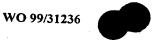
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Met	GIU	Thr	Leu	Tyr	Arg	Val	Pro	Phe	Leu	Val	Leu	Glu	Cvs	Pro	Asn	200
- 10	U				- 95					-90					-85	
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Leu	Lys	Leu	Lys	Lys	Pro	Pro	Trp	Leu	His	Met	Pro	Ser	Ala	Met	Thr	
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Glv	Gln	Tvr	att	Mot	Glu	gga	CCE	gca	CCC	agc	ttc	cta	ttt	aca	atg	346
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-	2		1	1	110	116	пец	z Asb	GIY	ser	Asn	АТА		Asn	Ile	
cca	aaa	ctc	aat	_	ttc	ctt	ctt	cta	++-	2++			10			
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Gly	Tyr	Leu	Met	Gly				-			50	3340	400	9944	ccg	242
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Lyaa	gage	ag c	agta	aaag	a aa	tatc	tagt	gaa	aaaa	cao	gaag	cata	tt a	2200	ttaas	665
CLag	adit	EC E	CCCC	ggta	t ta	aaga	gaca	aqt	ttat	cac	agaa	++++	t+ +	tect	actaa	725
ccca	Lugu	La L	acca	atga	t gt	tgagi	tggc	att	ttct	ttt	tagt	tttt	ca t	taaa	atata	785
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agig	ryry	at g	gtaga	atta	t tt	cagat	tatg	tate	gtaaa	aac	tatti	tacto	ga a	caat	aagat	1025
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<sup>&</sup>lt;212> DNA



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Met	Pro	Pne	HIS		Pro	Pne	Leu	GIA		Val	Cys	Leu	His	Leu	His	
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Leu	Thr	Pro		Leu	Thr	Val	Pro	Arg	Arg	Pro	Leu	Phe	Leu	Leu	Leu	
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His	Leu	Cys	Pro	His	Leu	Pro	Phe	Leu	Leu	Leu	Leu	Ser	Cys	Val	Gly	
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gkc	www	ccc	tcc	tgt	ctg	cct	tct	tcc	tcc	act	tgt	gtc	ago	ttg	cat	192
Xaa	Xaa	Pro	Ser	Cys	Leu	Pro	Ser	Ser	Ser	Thr	Cys	Val	Ser	Leu	His	
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				20												
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-25

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Gln Thr Asn Leu Ile Leu Phe Cys Val Gly Ala Val Gly Ala Cys Thr

-15

-10

-5

Ctc tct gtc aca caa ccg tgg tac cta gaa gtg gac tac act cat gag

146

Leu Ser Val Thr Gln Pro Trp Tyr Leu Glu Val Asp Tyr Thr His Glu

722

774

_	
•	,

180

195

			•													-
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WIC	vaı	- Ini	116	: Lys	Cys	Thr	Phe	Ser	: Ala 25	Thi	Gl	y Cys	Pro	Ser	Glu	· <del></del> -
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011	PIC	, 1111	35	. rea	Trp	Pne	: Arg	Tyr 40	Gly	Ala	His	Gln	Pro	Glu	Asn	
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Arg	Giu	тте	115	Leu	Leu	Ser	Lys	Glu 120	Leu	Arg	Ser	Phe	Leu	Thr	Ala	
Ctt	gta	tca	ctg	ctc	tct	gtc	tat	gtg	acc	ggt	gtg	tgc	gtg	qcc	ttc	530
Deu	val	130	ьеи	Leu	Ser	Val	Tyr 135	Val	Thr	Gly	Val	Cys	Val	Ala	Phe	
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Lys	Glu	Asp	Ser	Gln	Lys	Lys	Lys	Ser	Ala	Arg	Arg	Ile	Phe	Gln	Glu	
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للتراكب والمتبع فللتراكب والمراكب والمنافع والمتبع والمتبع والمتبعد والمراك والمتبع فياليا والمتباعد والمتباعد

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Ser Glu Lys Asp Asn Asn Thr Tyr Glu Asn Arg Arg Val Leu Ser Asn

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<211> 640

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<213> Homo sapiens

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tgg ttg gaa gta gaa tgt tcg ctg atg acc tgc aca acc tta ata aac Trp Leu Glu Val Glu Cys Ser Leu Met Thr Cys Thr Thr Leu Ile Asn -15 -10 -5	458
gca tcc gct atc tct aca aac act tta acc gac atg gga agt ttc gat Ala Ser Ala Ile Ser Thr Asn Thr Leu Thr Asp Met Gly Ser Phe Asp 1 5 10	506
aga aga gaa agc tgagaacttc ggaaaaggct catctgtcac cctggaraag Arg Arg Glu Ser	558
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ggc ttg cag atg ttc att cag agg aag ttt cca tac cct ttg cag tgg Gly Leu Gln Met Phe Ile Gln Arg Lys Phe Pro Tyr Pro Leu Gln Trp -25 -20 -15 -10	166
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539

599

637

40

taataaaggg gaacatttgg ccctgtgaaa aaaaaaaa



Thr Arg Val Glu	Ser Glu Lys Cy	s Asn Asn Leu	Trp Leu Phe Leu Glu	
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Thr Gly Gln Leu	Pro Lys Asp Ar	g Ser Thr Asp	Gln Xaa Ser	
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45

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                                   -10
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Thr Ser Ser His Ala Ser Ser Leu His Leu Pro Pro Ser Cys Thr Arg
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cct t Pro F																152
agg c Arg I	eu															200
tgt t Cys I 3																248
aat t Asn C 50																296
cag t Gln	gaa	actw	ıkk t	tcwc	ttct	a <b>a</b> a	gccc	ttca	ttt	ccca	caa	ggtt	aag	ctc		349
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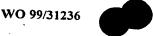
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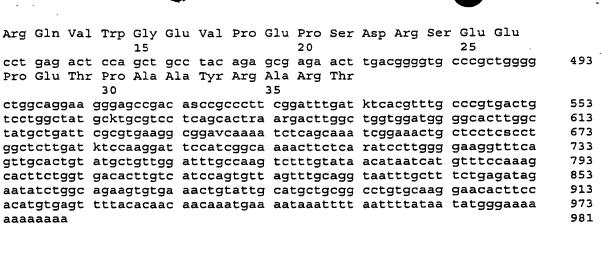
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440



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	GIu 2	Xaa Ser	Ala Pro	Xaa	Phe A	Ala Il	e Phe	Asn Pho	e Val	Gln	
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Ser Ile	Cys I		Val Ala	a Phe			r Asn	Tyr Let	ı Leu	Leu	
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His Trp			Val Met	: Val		Phe Gl	y Phe	Xaa Gly	/ Thr	Ile	
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, <b></b> ,	i.	LC DEU	OTH UIS	Set A	al A	eb hto	ьeu /	ar Leu	rne	ьeu	



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-25

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\_\_\_\_\_



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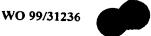
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TIE	G1u -5	Asp	Val	Pro	Phe	Thr 10	Glu	Lys	Asp		Glu 15	Asn	Gly	Pro	Gln	
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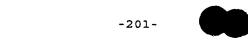
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Arg I	His I	lis	Ile	Leu	Gln	Gln	Phe	Len	Val	Ara	Tura	Com	919	g cca	CL	3	206
			15					20	vai	AT 9	пуь	ser	va. 25	L Pro	ьeт	1	
gaa a	aat g	gct	tca	ctt	cca	ttt	cct		cta	~~~	244		25		_		
Glu A	Asn A	lla	Ser	Leu	Pro	Phe	Pro	Hie	T.eu	230	agt Cor	Com	The	ייים נ	aaa	a.	254
	3	30					35		Deu	Gry	ser	40	пег	Pne	гуя	3	
att g	gtg g	gc	tgat	ttaa	tc r	tect		+	+ 000			40					
Ile V	/al c	ly		55						acts	, cta	ctgo	cct				303
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gcago	cctt	gt	tcaq	atat	a ca	gacc	ctta	tto	+~~	a+a	+				•		
acaca	ccct	t c	cacc	caaa	t ac	ctct	Gacc	CCS	2000	+~~	Lage	gtee	בב	grate	gtca	itg	363
agttt	gctt	a c	tcat	artc	a to	tect	####	C++	agge	cgg	aatg	9990	rg	grage	gara	ta	423
aatgg	attt	c to	atat	ggca	a ta	gart	aatt	772	ggca tass	+++	gett	CCCT	gc	ggtgt	cct	ca	483
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aactg	gage	C Ca	aaak	aaat	t cc	ctta	agac	229	266a	Laa Lab	tgte	aagg	ca	aggag	gta	aa	603
cctga	ggca	a to	aact	CCA	c cc	cttt	tcar	aag	acta ttta	-e-	caca	atar	aa	aatto	aat	tt	663
gtagt	ctat	or a	cato	gato	םם כ	atoc	taga	acg	ctta:	gtc	crgc	aaat	ag	catct	ttc	tt	723
gtagt	tgag	t ti	: t.t.t.1	tcca	7 62	acge	tagg ttox	900	ccta	999	gcaa	3999	ac	taaac	taa	at	783
caakt	gtaa	t ct		tec	9 22	3333		999	aggt	act	CSCT	gttg	at .	atttg	aca	ct	843
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gaatc	tara	cac	10225	200	- ~	calac	arac	ctgi	cttac	gtg	tttta	itca	ra o	cgtct	gtt	gt	1083
agttgi caacci	tota	a ac	gaac restt	29000	900	Jara:	aaaa	caco	cacat	gg .	ascct	gtaa	aa t	tgttt	ttg	ca	1143
caacct aat	-5040	~ 45	Juan	ع ما ما ت د	, ya	rkcgg	<sub>3</sub> cca	gtaa	aaaa	199	gtttt	acca	at t	taaa	aaaa	aa	1203
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                                                             -30
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Pro Thr Gly Lys Gln Leu Ala Asp Ile Gly Tyr Lys Thr Phe Ser Thr
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                                    -20
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Ser Met Met Leu Leu Thr Val Tyr Gly Gly Tyr Leu Cys Ser Val Arg
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Val	Tyr 5	His	Tyr	Phe	Gln	Trp	Arg	Arg	Ala	Gln	Arg	Gln	Ala	Ala	Glu	
Glu	cag Gln	aag Lys	dac Xaa	tca Ser	Gly	atc	atg Met	tag	aact	999		tttt	tc t	cctg	agcar	315
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cago	ageg	t c c	atgg		ca a	accc	tgtt	g ga	agaa	agtg	ccc	atgg	ttt	ctct	ggttct	435
900	artt	iga i	cagt	ctat	gg a:	rgct	tttg	a at	cgta	atar	caa	tgtg	agg	gtga	rgtaca	495
CCL	acay	aca	LLdd	ataa	בל בי	gctg	tgtc	a aa	aaaa	aaaa	a					536
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	2 > D															
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	S	ed Pi	LITA	ILA	/AVG/	/FP										
				_												
		002 DIÀY	sigr	nal												•
< 2 2 2	اد د>	30	05													
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	. J.		, ,			•										
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			_	_		_								Leu		
									4 -	-15	,				-10	
aca	gcc	atc	ttg	gca	gtg	gct	gtw	ggt	ttc	cca	atc	tct	caa	gac		161
Thr	Ala	Ile	Leu	Ala	Val	Ala	Val	Gly	Phe	Pro	Val	Ser	Gln	Asp	Gln	
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Glu	Arg	Glu	Lys	Arg	Ser	Ile	Ser	Asp	Ser	Asp	Glu	Leu	Āla	Ser	Gly	
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Xaa	Phe	Val	Phe	Pro	Tyr	Pro	Tyr	Pro	Phe	Arg	Pro	Leu	Pro	Pro	Ile	
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cca -	ttt	cca	aga	ttt	cca	tgg	ttt	aga	cgt	aat	ttt	cct	att	cca	ata	305
Pro	Phe	Pro	Arg	Phe		Trp	Phe	Arg	Arg		Phe	Pro	Ile	Pro	Ile	
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CCE	gaa	tct	gcc	cct	aca	act	ccc	ctt	cct	agc	gaa	aag	taa	acaar	aa	354
PLO	GIU	ser	Ala		Thr	Thr	Pro	Leu	Pro	Ser	Glu	Lys				
~~~ -				60					65							
gyaa	aagt	ca c	rata	aacc	T 99	cac	ctga	aat	tgaa	att	gago	cact	tc (	cttga	araat	414
caad	a + - +	or g	ttaa	caaa	a ra	aaaa	caaa	tgt	aatt	gaa	atac	gcaca	ca g	gcatt	ctcta	474
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пуъ	-15	vaı	Leu	Leu	Leu	11e -10	Thr	Ala	Ile	Leu	Ala	Val	Ala	Val	Gly	107
ttc	cca	gtc	tct	caa	gac	cak	gaa	cqa	gaa	aaa	aga	agt	atc	agt	gac	155
Phe	Pro	Val	Ser	Gln	Asp	Xaa	Glu	Ara	Glu	Laze	7~~	Eo.	710	Com	Asp	122
_				5					10					15		
agc	gat	gaa	tta	gct	tca	999	ttt	ttt	gtg	ttc	cct	tac	cca	tat	cca	203
Ser	Asp	Glu	Leu	Ala	Ser	Gly	Phe	Phe	Val	Phe	Pro	Tvr	Pro	Tyr	Pro	203
			20					25				- 7	30	-3-	110	
ttt	cgc	cca	ctt	cca	cca	att	cca	ttt	CCa	ara	+++	<b>663</b>	+~~			
Phe	Arg	Pro	Leu	Pro	Pro	Tle	Dro	Dhe	Dro	aya aya	72-	Door	rgg	-1	aga	251
		33					40					45				
cgt	aat	ttt	cct	att	cca	ata	cct	gaa	tct	acc	cct	aca	act	ccc	ctt	299
Arg	Asn	Phe	Pro	Ile	Pro	Ile	Pro	Glu	Ser	Δla	Pro	Thr	Thr	Dro	Ton	233
	50					55					60				ьeu	
ccg	agc	gaa	aag	taaa	caag	aa c	gaaa	agto	a co	ataa	acct	aat	cacc	rtas		351
Pro	Ser	Glu	Lys		_	_	_	_	~	,		75-		. cga		331
65																
aatt	gaaa	tt a	aacc	actt	c ct	taar	craat				~++-				acaaa	
tgta	atto	aa a	tage	acac	2 00	2541	+ <+ >	~			gcta	acaa	aa g	jaaaa	acaaa	411
acat	gaaa	ac =	2222	2222	a aa	acti	ccta	gto	aata	tct	ttag	tgat	ct t	cttt	aataa	471
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Cys Ser Tyr Ala Thr Arg Arg Ser Pro Ser Glu Leu Ser Leu Leu Pro	
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age tee etg tgg gte eta gee aca age tet eca aca att act att gea	209
Ser Ser Leu Trp Val Leu Ala Thr Ser Ser Pro Thr Ile Thr Ile Ala	
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ctc gcg atg gcc gcc ggg aat ctg tgc ccc ctt cca tca tca tkt cgt	257
Leu Ala Met Ala Ala Gly Asn Leu Cys Pro Leu Pro Ser Ser Xaa Arg	
10 15 20 25	
crc aaa agg cgc tgg tgt cag gca asc car caa ara gct ctg ctg	302
Xaa Lys Arg Arg Trp Cys Gln Ala Xaa Gln Gln Xaa Ala Leu Leu	
30 35 40	
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cctcggacca gccttacctg tgacactgca ccctcacggc cacccgacta ctttgcctcc	422
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agg ggc aag gtg aaa act gct cct att ccc atc tct agg ttt cct ttc	223
Arg Gly Lys Val Lys Thr Ala Pro Ile Pro Ile Ser Arg Phe Pro Phe -50 -45	
*·	
ctc cct acc cac gac cca ccc acc cca gca cat tgg tct cca gca tct	271
Leu Pro Thr His Asp Pro Pro Thr Pro Ala His Trp Ser Pro Ala Ser	
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cat cag cag ttt aaa cat kkg tca ccc ctc ctc act ttg gcc ctg ctg	319
His Gln Gln Phe Lys His Xaa Ser Pro Leu Leu Thr Leu Ala Leu Leu -15 -10 -5	
-15 -10 -5 ggt cag tgc tct ctg ttc arc aat ttg agg aaa aaa ctt gca ggg caa	
as as one con one are are acting agg and and cot god ggg can	267
Gly Gln Cys Ser Len Phe Xaa Ach Len Are too too Ale Cle Cl-	367
Gly Gln Cys Ser Leu Phe Xaa Asn Leu Arg Lys Lys Leu Ala Gly Gln	367
Gly Gln Cys Ser Leu Phe Xaa Asn Leu Arg Lys Lys Leu Ala Gly Gln  1 5 10 aaa gca aaa aaa tta cct tcc tcc agc ctg ccc ctg aca ctc tgg	367 415



Lys Ala Lys Lys Leu Pro Ser Phe Ser Ser Leu Pro Leu Thr Leu Trp 15 20 25	
cca tta act cct caa ttt gct gag ctc act aca gtg gca caa aaa aaa	463
Pro Leu Thr Pro Gin Phe Ala Glu Leu Thr Thr Val Ala Gln Lys Lys  30 40 45	
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Leu Arg Trp Ser Gly Thr Leu Gly Trp Gly Pro Val Pro Ser Trp Val  50 55 60	
caa ttt ttt tta ggg tgaatggagg garagttggg gactgaaaas ccttcaaara	566
GIN FRE FRE Leu GIY	
65 	
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tatggtcaac cgcttggaaa atakttgaac acagtacaat aaratatttt gaggctggga	686
ktggtggctc atgcctgtaa taatcccagg actttgtgar accaaktttg aaggatcact	746
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atycallyca tagitgatca agicactete tggcetaaaa cetteetigg efectioning	180
coeccaggat adagtotgga cocotcago atg got tgt gag act cat ggt gto	233
Met Ala Cys Glu Thr His Gly Val	
-30 -25	
Lev Vol Dro 37 and the tet ggt etc ate act tge ett ett gea tte	281
hed val Pro Ala His Leu Ser Gly Leu Ile Thr Cys Leu Leu Ala Phe	
-15 -10	
tgg gtc cca gcc tcc tgt atc cag aga tgc agt ggc tct cca ttg cca	329
Tip val Pro Aia Ser Cys Ile Gln Arg Cys Ser Gly Ser Pro Leu Pro	525
· = · · = <sup>-</sup> - · · · · · · · · · · · · · · · · · ·	
ctc tgattcctcc tttcttttgg tcacagagaa agggtacttt ctctgtcaaa Leu	382
totcaactta gacttgactt cotccaagga gotttggota tactototo cwcgacccc	4.45
accetggeat actacacara teactetggg eteacttgee tgeetaatgg teateteece	442
agtaaactgt aagctccttg agggcaagga ttgtgttgga atttttgtat taacagtgcc	502
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aaa

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                                                                       180
tacatcatat gtggaggaca cttatgctgt g atg gcc cca cac aca gct tcc
                                    Met Ala Pro His Thr Ala Ser
                                        -35
ttt ggg gtc tgt ccc ctg ctc tcc gtt acc cgc gtg gta gcc act gag
                                                                      280
Phe Gly Val Cys Pro Leu Leu Ser Val Thr Arg Val Val Ala Thr Glu
                -25
                                     -20
cac tgg ctc ttc ctg gct tca ctc tct ggc atc aaa act tat cag tcc
                                                                      328
His Trp Leu Phe Leu Ala Ser Leu Ser Gly Ile Lys Thr Tyr Gln Ser
            -10
                                -5
tac atc tca gtc ttt tgc aag gtg aca ctt atc tgattaccta attcacacra
Tyr Ile Ser Val Phe Cys Lys Val Thr Leu Ile
                                                                      381
                        10
aggtgttaat ggtggtaatg gcataktatt tattacccca ggggacccak aacggtggta
                                                                      441
tcaaaacata tcattcccca gtggtttaaa actctggtag ctttccargg aatccaaagt
                                                                      501
ggaatccagt ctccttagct gawttcacag ggccccgtct gcacaacttg gcttctgtcg
getteectan ecetgaette ecaageetta gteateacee teteteecae ecagggetea
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aaa
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                                                                    110
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 atg ctg ggc gca rgg gct ggc gtg ggc tac gcg ctc ctc gtt atc gtg
 Met Leu Gly Ala Xaa Ala Gly Val Gly Tyr Ala Leu Leu Val Ile Val
                                                                    158
 acc ccg gga gag cgg cgg aag cag gaa atg cta aag gag atg cca ctg
 Thr Pro Gly Glu Arg Arg Lys Gln Glu Met Leu Lys Glu Met Pro Leu
                                                                    206
                15
                                    20
Gln Asp Pro Arg Ser Arg Glu Glu Ala Ala Arg Thr Gln Gln Leu Leu
                                                                    254
            30
ctg gec act ctg cag gag gca gcg acc acg cag gag aac gtg gcc tgg
Leu Ala Thr Leu Gln Glu Ala Ala Thr Thr Gln Glu Asn Val Ala Trp
                                                                    302
                           50
agg aag aac tgg atg gtt ggc ggc gaa ggc ggc gcc acg gga kgt cac
Arg Lys Asn Trp Met Val Gly Gly Glu Gly Gly Ala Thr Gly Xaa His
                                                                    350
    60
                       65
cgt gag acc gga ctt gcc tcc gtg ggc gcc gga cct tgg ctt ggg cgc
Arg Glu Thr Gly Leu Ala Ser Val Gly Ala Gly Pro Trp Leu Gly Arg
                                                                   398
                   80
                                       85
agg aat ccg agg cag ctt tct cct tcg tgg gcc can cgg aaa atc cgg
Arg Asn Pro Arg Gln Leu Ser Pro Ser Trp Ala Xaa Arg Lys Ile Arg
                                                                   446
               95
                                   100
amc gaa aat wcc atg cca gga ctc tcc ggg gtc ctg tgaactgccg
Xaa Glu Asn Xaa Met Pro Gly Leu Ser Gly Val Leu
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                               115
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cagggccgag acgcgagtcg gatgtggtga actgaaagaa ccaataaaat catgttcctc
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751

811

813



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Ala	Pro	ctg Leu -60	Ser	Cys	Leu	Ser	Pro	Thr	Lys	Trp	Ser	Ser -50	Val	Ser	Ser	106
Ala	Asp -45	tca Ser	Thr	Glu	Lys	Ser	Ala	Ser	Ala	Ala	Gly -35	Thr	Arg	Asn	Leu	154
Pro -30	Phe	cag Gln	Phe	Cys	Leu -25	Arg	Gln	Ala	Leu	Arg	Met	Lys	Ala	Ala	Gly -15	202
Ile	Leu	acc Thr	Leu	Ile	Gly	Cys	Leu	Val	Thr	Gly	Val	Glu	Ser	Lys 1	Ile	250
Tyr	Thr	cgt Arg 5	Cys	Lys	Leu	Ala	Lys 10	Ile	Phe	Ser	Arg	Ala 15	Gly	Leu	Asp	298
Asn	Xaa 20	agg Arg	Gly	Phe	Ser	Leu 25	Gly	Asn	Trp	Ile	Cys 30	Met	Ala	Tyr	Tyr	346
Glu 35	Ser	ggc Gly	Tyr	Asn	Thr 40	Thr	Ala	Gln	Thr	Val 45	Leu	Asp	Asp	Gly	Ser 50	394
atc Ile	gac Asp	tay Tyr	ggc	atc Ile 55	ttc Phe	caa Gln	atc Ile	aac Asn	agc Ser 60	ttc Phe	gcg Ala	tgg Trp	tgc Cys	aga Arg 65	cgc Arg	442
gga Gly	aag Lys	ctg Leu	aag Lys 70	gag Glu	aac Asn	aac Asn	cac His	tgc Cys 75	cay His	gtc Val	gcc Ala	tgc Cys	tca Ser 80	gcc Ala	ttg Leu	490
rtc Xaa	act Thr	gat Asp 85	gac Asp	ctc Leu	aca Thr	gat Asp	gca Ala 90	att Ile	atc Ile	tgt Cys	gcc Ala	arg Xaa 95	aaa Lys	att Ile	gtt Val	538
aaa Lys	gag Glu 100	aca Thr	caa Gln	gga Gly	atg Met	aac Asn 105	tat Tyr	tgg Trp	caa Gln	ggc	tgg Trp 110	aag Lys	aaa Lys	cay His	tgt Cys	586

gag ggg aga gac ctg tcc gas tgg aaa aaa ggc tgt gag gtt tcc

Glu Gly Arg Asp Leu Ser Xaa Trp Lys Lys Gly Cys Glu Val Ser

taaactggaa ctggacccag gatgctttgc ascaacgccc tagggtttgc agtgaatgtc

caaatgcctg tgtcatcttg tcccgtttcc tcccaatatt ccttctcaaa cttggagagg

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125

120

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<221> sig\_peptide

<222> 154..360

<223> Von Heijne matrix score 4.80000019073486 seq MMVLSLGIILASA/SF



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<221> polyA\_site <222> 763..775

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													11 -	O Va	T BLO	
aa+	~~~												- 6	5		
700	gag	acc mb	atc	ata	gtg	ctc	cca	tca	aat	gto	ato	aac	tto	tcc	caa	222
ASII	GIU		110	Ile	Val	Leu	Pro	Ser	Asn	Val	Ile	aac Asn	Phe	Ser	Gln	
gca	gag	aaa	ccc	gaa	CCC	acc	aac	cag	aaa	cad	gat		cta	220		0.50
Ala	Glu	Lys	\ Pro	Glu	Pro	Thr	Asn	Gln	Glv	Gln	Aen	agc Ser	Tou	T	ada T	270
						- <del>4</del> U					2 -					
cat	cta	cac	gca	gaa	atc	aaa	att	att	aaa	20+		cag				
His	Leu	His	Ala	Glu	Ile	Lvs	Val	Tle	222	Th.	alc Tla	cag Gln	atc	ttg	tgt	318
-30					-25	-7-			Gry	THI	тте	Gin	lle	Leu		
ggc	atq	ato	qta	tta	200	++~	~~~			-20		tct			-15	
Gly	Met	Met	Val	T.eu	Ser	Ley	999	alc	att	ttg	gca	tct	gct	tcc	ttc	366
•				-10	Ser	Deu	GIY	TIE	TIE	Leu	Ala	Ser	Ala	Ser	Phe	
				- x o					- 5					_		
Ser	Dro	λαπ	Dha	acc	caa	grg	act	tct	aca	ctg	ttg	aac	tct	gct	tac	414
561	110		Pne	Inr	Gin	Val	Thr	Ser	Thr	Leu	Leu	aac Asn	Ser	Ala	Tvr	
		_					111									
CCa	EEC	ata	gga	CCC	ttt	ttt	gtr	akt	aaa	btt	tct	gag	gag	aac	agg	462
Pro		IIe	Gly	Pro	Phe	Phe	Val	Xaa	Lys	Xaa	Ser	gag Glu	Glu	Glv	722	402
						23					3 0					
atg	999	caa	ara	999	gag	gaa	rat	vcc	aat	agc		aac	++0			
Met	Gly	Gln	Xaa	Gly	Glu	Glu	Xaa	Xaa	Asn	Ser	Len	aac Asn	Dha	D	SCC	510
					~± U					4 E						
gcc	agc	ttg	cta	tkt	tta	atc	tac	cac	~~~	~		ttc			50	
Ala	Ser	Leu	Leu	Xaa	Len	Tle	Cve	Cla	yav Va-	Caa	gga	Phe .	aac	ggt	gaa	558
				55			Cys	GIII	naa Co	GIN	GIY	Phe .			Glu	
tct	tat	tet			~~~				60					65		
Ser	Cvs	Ser	Dro '	9 C C	333	carg	ataa	ca g	gggt	tgct	t ra	tttt	agat			606
	<b>-</b>		70	val	сту											
caat	++~+															
tost		La C	caga	ctcaa	a ata	aaac	attt	ctt	ttga	aaa	tcat	cttai	t c	ttca	catta	666
				2 - 446	a aau	Lau	CDAS	KTC		~~~					catta aaatc	726
catg	aatta	ag g	ataa	agtt	g gga	aagga	aaca	ttt	tata	caa	aaaa:	aaaaa	ah c			
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aac	cgtt	gat	ggga	ctga	ga a	acca	gagt:	k aa	aacc	tctt	tgg	agct	tot g	gagga	actcag	120
															ccc	174
										_				_	l Pro	
													-6			
aat	gag	acc	atc	ata	ata	ctc	cca	tca	aat	atc	atc	220	_	tcc	C22	222
														Ser		222
ASII	GIU	-60	110	116	Vai	meu		Ser	ASII	vai	116		Pile	Ser	GIII	
							-55					-50				
gca	gag	aaa	ccc	gaa	CCC	acc	aac	cag	333	cag	gat	agc	ctg	aag	aaa	270
Ala	GIu	Lys	Pro	Glu	Pro	Thr	Asn	Gln	Gly	Gln	Asp	Ser	Leu	Lys	Lys	
	-45					-40					-35					
cat	cta	cac	\gca	gar	rtc	aaa	gtt	att	ggg	act	atc	cag	atc	ttg	tgt	318
														Leu		
-30					-25	-			•	-20					-15	
aac	ato	ato	ota	tta	agc	tta	aaa	atc	att		aca	tct	act	tcc		366
GIV	Met	Met	Val	T.eu	Ser	Leu	222	Tle	Tle	Lev	712	502	מכב	Ser	Dho	300
<b>U</b> -1			• • • •	-10	561	204	Cly	110	-5	Dea.	ATA	261	ATO	_	FILE	
+ = +									_					1	À	
200	Door	aat	71.	acc	caa	grg	act	- CC	aca	ctg	ttg	aac	ECE	gct	tac	414
ser	Pro		Pne	Thr	Gin	Val		Ser	Thr	Leu	Leu		Ser	Ala	Tyr	
		5					10					15				
														tca		462
Pro	Phe	Ile	Gly	Pro	Phe	Phe	Phe	Ile	Ile	Ser	Gly	Ser	Leu	Ser	Ile	
	20					25					30					
qcc	aca	aaa	aaa	agg	tta	acc	aac	ctt	tta	ata	cat	acc	acc	ctg	att	510
														Leu		310
35		-1-	-,-	5	40		*****		200	45	1115	T 111	1111	шси	50	
	200	a++	ata	24+		a+-	+									
994	Com	TIO	Tou	agu	37-	teg	CCC	gee	clg	grg	ggt	ttc	act	ayc	ctg	558
Gly	261	116	ьeu		Ala	ьeu	Ser	Ala		val	GIY	Pne	Ile	Xaa	Leu	
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tct	gtc	aaa	cag	gcc	acc	tta	aat	cct	gcc	tca	ctg	cak	tgt	gag	ttg	606
Ser	Val	Lys	Gln	Ala	Thr	Leu	Asn	Pro	Ala	Ser	Leu	Xaa	Cys	Glu	Leu	
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gmc	aaa	aat	aat	ata	cca	aca	ara	akt	tat	gtt	yct	tac	ttt	tat	cat	654
														Tyr		
	_	85					90		4			95		- 2 -		
gat	tca	ctt	tat	acc	acq	gac		tat	aca	acc	222		akt	ctg	act	702
														Leu		702
p	100	Leu	- 7 -	1111	1111	105	naa	TYL	1111	MIA	_	AIA	naa	ьeu	Ala	
~~~											110					
														tgc		750
	THE	ьeu	ser	Leu		Leu	lle	Cys	Thr		Leu	Glu	Phe	Cys	Xaa	
115					120					125					130	
sct	gtg	ctc	act	gct	gtg	ctg	cgg	tgg	aaa	cag	gct	tac	tct	gac	ttc	798
Xaa	Val	Leu	Thr	Ala	Val	Leu	Arg	Trp	Lys	Gln	Ala	Tyr	Ser	Asp	Phe	
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cct	ggg	aqt	qta	ctt	ttc	cta	cct	cam	agt	tac	att	aaw	aat	tct	aam	846
Pro	Glv	Ser	Val	Len	Phe	Len	Pro	Xaa	Ser	TVY	Tle	GIV	Δen	Ser	GJV	
	4		150					155		- 7 -		<b>C T y</b>	160	501	<b>U</b>	
ato	tcc	tes		a+~	2011	as+	~		~~~	+	~				a.e.t	0.04
														ttg		894
met	ser		гÀг	met	Inr	Hls		Cys	GIA	Tyr	GIU		Leu	Leu	Thr	
4		165					170					175				
	taag	gaaa	aaa g	gggag	gaaat	a tt	taato	cagaa	agt	tgat	tct	tate	gataa	ata		947
Ser																
tgga	aaaag	gtt a	aacca	attat	a ga	aaaag	gcaaa	gct	tgag	gttt	ccta	aato	gta a	agctt	ttaaa	1007
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                                                                    120
 ctttcatttc attctagaag acccc atg caa gtt ccc cac cta agg gtc tgg
                                                                    172
                            Met Gln Val Pro His Leu Arg Val Trp
                                -35
 aca cag gtg awa gat acc ttc att ggt tat aga aat ttg gga ttt aca
                                                                    220
 Thr Gln Val Xaa Asp Thr Phe Ile Gly Tyr Arg Asn Leu Gly Phe Thr
         -25
                            -20
 agt atg tgc ata ttg ttc cac tgt ctt ctt agc ttt cag gtt ttc aaa
                                                                    268
 Ser Met Cys Ile Leu Phe His Cys Leu Leu Ser Phe Gln Val Phe Lys
                        -5
aag aaa aga aaa ctt ara ctt ttc tgatgttctt ttttacgtaa ataaccattt
                                                                    322
 Lys Lys Arg Lys Leu Xaa Leu Phe
                10
tattgttgtt ttgctttttc tgccttcaaa ctactcccac aggccaaata tavctggctg
                                                                    382
cttctttctg taaataaagt tttattgggc cacagccatg gccatctttt aaaaaaaaa
                                                                    442
aa
                                                                    444
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score 7.5

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ttttg atg gtg gcc ctg aac ctc att ctg gtt ccc tgc tgc gct tgg Met Val Ala Leu Asn Leu Ile Leu Val Pro Cys Cys Ala Ala Trp	120 170
-10 -5 1	
tgt gac cca cgg agg atc cac tcc cag gat gac gtg ctc cgt agc tct Cys Asp Pro Arg Arg Ile His Ser Gln Asp Asp Val Leu Arg Ser Ser 5 10 15	218
gct gct gat act ggg tct gcg atg cag cgg cgt gag gcc tgg gct ggt	266
Ala Ala Asp Thr Gly Ser Ala Met Gln Arg Arg Glu Ala Trp Ala Gly 20 25 30	
tgg aga agg tca caa ccc ttc tct gtt ggt ctg cct tct gct gaa aga Trp Arg Arg Ser Gln Pro Phe Ser Val Gly Leu Pro Ser Ala Glu Arg 35 40 45	314
ctc gag aac caa cca ggg aag ctg tcc tgg agg tcc ctg gtc gga gag	362
Leu Glu Asn Gln Pro Gly Lys Leu Ser Trp Arg Ser Leu Val Gly Glu 50 55 60 65	302
gga cat aga atc tgt gac ctc tgacrrctgt gaasccaccc tgggctacar Gly His Arg Ile Cys Asp Leu	413
70 aaaccacagt cttcccagca attattacaa ttcttgaatt ccttggggat tttttactgc	477
cctttcaaag cacttaaktg tkrratctaa cgtkttccag tgtctgtctg aggtgactta	473 533
aaaaatcaga acaaaacttc tattatccag agtcatggga gagtacaccc tttccaggaa	593
taatgttttg ggaaacactg aaatgaaatc ttcccagtat tataaattgt gtatttaaaa	653
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-55 -50 -45	
atc cca gtt cct cca agg ggc ctg ggt gct ggg gag ggg tca ggt agt	158
Ile Pro Val Pro Pro Arg Gly Leu Gly Ala Gly Glu Gly Ser Gly Ser	
-40 -35 -30 cca gtg cgt cca cct gta tcc acc tgg ggc cct agc tgg gcc cag ctc	206
Pro Val Arg Pro Pro Val Ser Thr Trp Gly Pro Ser Trp Ala Gln Leu	200



-25 -20 -15	
ctg gac agt gtc cta tgg ctg ggg gca cta gga ctg aca atc cag gca	254
Leu Asp Ser Val Leu Trp Leu Gly Ala Leu Gly Leu Thr Ile Gln Ala	
gto ttt too acc act ggc cca gcc ctg ctg ctt ctg gtc agc ttc	
Val Phe Ser Thr Thr Gly Pro Ala Leu Leu Leu Leu Val Ser Phe	302
10 15 20	
ctc acc ttt gac ctg ctc cat agg ccc gca gtc aca ctc tgc cac agc	350
Leu Thr Phe Asp Leu Leu His Arg Pro Ala Val Thr Leu Cys His Ser	350
25 30 35	
gca aac ttc tca cca ggg qcc aga gtc agg ggg ccg gtg aag gtc ctg	398
Ala Asn Phe Ser Pro Gly Ala Arg Val Arg Gly Pro Val Lys Val Leu	
45 50	
gac agc agg agg ctc tac tcc tgc aaa tgg gta cag tct cag gac aac	446
Asp Set Arg Arg Leu Tyr Ser Cys Lys Trp Val Gln Ser Gln Asp Asp	110
55 60 65	
tta gee tee agg aag cae tge tge tge tea tgg gge tgg gee ege	494
hed Ald Sel Alg Lys His Cys Cys Cys Ser Trp Gly Trp Ala Arg	
75 80 85	
tcc tgaaaacctg tggcatgccc ttgwaccctg cttggcctgg ctttctgcct	547
SEI .	
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bed BABIRCIEPEAVA/SA	
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Met Glu Arg	
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Leu Val Leu Thr Leu Cys Thr Leu Pro Leu Ala Val Ala Ser Ala Gly	105
tgc gcc acg cca gct cgc aac ctg agc tgc tac cag tgc ttc aag	
Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln Cys Phe Lys	153
5 10 Ala Alg Ash bed Ser Cys Tyr Gin Cys Phe Lys	
gtc agc tgg acg gag tgc ccg ccc acc tgg tgc agc ccg ctg gac	
Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser Pro Leu Asp	201
Caa gto tgo ato too aac gag gtg gto gto tot tit agt gag toy coo	
Gln Val Cys Ile Ser Asn Glu Val Val Ser Phe Ser Glu Ser Pro	249
var var var ser pre ser gru ser pro	

4	
7	

				40					45					50			
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PIO	GIY	Arg	Gly 55	хаа	vaı	Pro	хаа	Ala 60	GIÀ	GIu	Xaa	Pro	Val .65	Pro	Pro		
cct	ctc	wkc	gac	tta	bct	atg	act	cct	cgg	ckc	усс	agg	gcc	tgg	ggc		345
Pro	Leu	Xaa 70	Asp	Leu	Xaa	Met	Thr 75	Pro	Arg	Xaa	Xaa	Arg 80	Ala	Trp	Gly		
cck	gtg	ggt	ccd	aaa	gtg	cct	cct	gct	gtc	tct	ccc	aca	ctq	aac	tca		393
Pro	Val	Gly	Pro	Lys	Val	Pro	Pro	Ala	Val	Ser	Pro	Ala	Leu	Gly	Ser		
	85					90					95			-			
ggc	gag	cat	ccs	rva	btg	tgaa	tkkk	ga d	tttt	ttct	c ck	ccat	ttga	a			441
	Glu	His	Pro	Xaa	Xaa												
100					105												
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															attg		681
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tgc Cys	gcc Ala 5	acg Thr	acg Thr	cca Pro	gct Ala	cgc Arg 10	aac Asn	ctg Leu	agc Ser	tgc Cys	tac Tyr 15	cag Gln	tgc Cys	ttc Phe	aag Lys	153
Val 20	Ser	Ser	Trp	Thr	Glu 25	Cys	ccg Pro	Pro	Thr	Trp 30	Cys	Ser	Pro	Leu	Asp 35	201
Caa Gln	gtc Val	tgc Cys	atc Ile	tcc Ser 40	aac Asn	gag Glu	gtg Val	gtc Val	gtc Val 45	tct Ser	ttt Phe	aaa Lys	tgg Trp	agt Ser 50	gta Val	249
cgc Arg	gtc Val	L <b>e</b> u	ctc Leu 55	agc Ser	aaa Lys	cgc Arg	tgt Cys	gct Ala 60	ccc Pro	aga Arg	tgt Cys	ccc Pro	aac Asn 65	gac Asp	aac Asn	297

•			,												• `	
atg Met	aak Xaa	ttc Phe 70	gaa Glu	tgg Trp	tcg Ser	ccg Pro	gcc Ala	ccc Pro	atg Met	gtg Val	caa Gln	ggc Gly	gtg Val	atc Ile	acc Thr	<b>345</b>
agg	cgc	tgc	tgt	tcc	tgg	gct	ctc	tgc	aac	agg	gca	ctg	acc	cca	cag	393

Arg Arg Cys Cys Ser Trp Ala Leu Cys Asn Arg Ala Leu Thr Pro Gln 90 95 gag ggg cgc tgg gcc ctg cra ggg ggg ctc ctg ctc cag gac cct tcg Glu Gly Arg Trp Ala Leu Xaa Gly Gly Leu Leu Gln Asp Pro Ser 110

agg ggc ara aaa acc tgg gtg cgg cca cag ctg ggg ctc cca ctc tgc 489 Arg Gly Xaa Lys Thr Trp Val Arg Pro Gln Leu Gly Leu Pro Leu Cys 120

125 ctt ccc awt tcc aac ccc ctc tgc cca rgg gaa acc cag gaa gga 534 Leu Pro Xaa Ser Asn Pro Leu Cys Pro Xaa Glu Thr Gln Glu Gly 140

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	nis	Pne	1rp	Asp	Gly	Lys	Gly	Cys 45	Glu	Met	Ile	Cys	Tyr 50	Cys	Asn	Phe	
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	пуs	55	ııe	Ala	Leu	Leu	Pro 60	Lys	Arg	Arg	Phe	Leu 65	Trp	Thr	Lys	Asp	300
	ctc	ttt	cgt	gat	tcc	ttg	caa	caa	tca	atg	aga	atc	ttc	atg	tat	tct	400

Leu 70	Phe	Arg	Asp	Ser	Leu 75	Gln	Gln	Ser	Met	Arg 80	Ile	Phe	Met	Tyr	Ser 85	
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Ser	Arg	Gly 5	Phe	Pro	Leu	Arg	Leu 10	Gln	Ala	Thr	Glu	Val 15	Arg	Ile	Cys	
cct	gtg	gaa	ttc	aac	CCC	aac	ttc	gtg	gcg	cgt	atg	ata	cct	aaa	gtg	202
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	Trp	Ser	Ala	Phe	Leu	Glu	Ala	Xaa	Asp	Asn	Leu	Arg	Leu	Ile	Gln	
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Val	Pro	Arg	Arg		Gly											
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Gln	Arg 20	Phe	Phe	Ala	Leu	Leu 25	Thr	Pro	Thr	Trp	Lys 30	Ala	Glu	act Thr	Thr	197
Cys 35	Arg	Leu	Arg	Ala	Thr 40	His	Gly	Суѕ	Arg	Asn 45	Pro	Thr	Leu	gtc Val	Gln 50	245
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1 5 10	
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Gry Ara Ara Gry Leu Lys Ala Ala Gln Gly Pro Pro Ala Pro Ala	
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Val Pro Pro Asn Thr Xaa Val Met Ala Cys Thr Gln Thr Ala Leu Leu	
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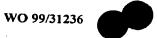
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Met Ile Leu Cys Phe Leu Leu Pro His His -15 -10	
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Arg Leu Gln Glu Ala Arg Gln Ile Gln Val Leu Lys Met Leu Pro Arg -5 1 5 10	
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Glu Lys Leu Arg Arg Glu Glu Arg Lys Gln Ile Asn Gly Lys Lys 15 20 25	
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Gly Asn Xaa Xaa Xaa Xaa Leu Ser Lys Arg Asp 45 50 55	
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60

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	Gly	Glu	Thr	Met	Asp 80	Leu	Gln	His	Gly	Ser 85	Pro	Phe	Thr	Lys	Met 90	Pro	)	,
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325



330

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WO 99/31236

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cccg	gcggt	at.	cktca	acagt	g at	ccgg	gago	t tgg	gacta	acga	taco	cacro	cmg g	gccta	accagc	617
tcwc	ggto	wa	cgcca	acaga	at ca	agac	caara	a cca	aggc	ctct	gtco	caccs	stg 9	gccaa	acttgg	677
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Met Gly Glu Ala Ser Pro Pro Ala	
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ccc gca agg cgg cat ctg ctg gtc ctg ctg ctc ctc tct acc ctg	161
Pro Ala Arg Arg His Leu Leu Val Leu Leu Leu Leu Ser Thr Leu	
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Val Ile Pro Ser Ala Ala Ala Pro Ile His Asp Ala Asp Ala Gln Glu	
-5 1 5 10	
ago too tig ggt oto aca ggo oto cag ago ota oto caa ggo tio ago	257
Ser Ser Leu Gly Leu Thr Gly Leu Gln Ser Leu Leu Gln Gly Phe Ser	
15 20 25	
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Arg	Leu	Phe	Leu 30	Lys	Gly	Asn	Leu	Leu 35	Arg	Gly	Ile	Asp	Ser	Leu	Phe		
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Ser	Ala	Pro	Met	Āsp	Phe	Ara	Glv	Leu	Pro	Glv	Asn	Tyr	Hie	Lve	Glu		233
		45		•			50			,		55	****	Lys	Olu		
gag	aac	caq	gag	cac	cag	cta		aac	aac	acc	ctc		200	C= C	ctc		401
Glu	Asn	Gln	Glu	His	Gln	Leu	Glv	Asn	Asn	Thr	T.e.ii	Ser	Ser	Tic	Leu		4 O T
	60					65	1				70	501	561	1113	neu		
cag	atc	gac	aaq	atq	acc		aac	aac	aca	aaa		ata	ctc	- 	tac		449
Gln	Ile	Asp	Lvs	Met	Thr	Asp	Asn	Lvs	Thr	Glv	Glu	Val	T.eu	TIE	Sex		449
75		-	•		80	_		-1-		85	014	Vul	Deu	110	90		
gag	aat	gtg	gtg	qca	tcc	att	caa	cca	vca		ggg	anc	ttc	gag	aat	·	497
Glu	Asn	Val	Val	Ala	Ser	Ile	Gln	Pro	Xaa	Glu	Glv	Xaa	Phe	Glu	Glv		<del>4</del> 31
				95					100				1 110	105	Cly		
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Asp	Leu	Lys	Val	Pro	Arg	Met	Glu	Glu	Lvs	Glu	Ala	Leu	Val	Pro	Xaa		242
			.110		_			115	-2-				120		nau		
car	aag	gcc	acg	gac	agc	ttc	cac	aca	gaa	ctc	cat	ccc		ata	acc		593
Gln	Lys	Ala	Thr	Asp	Ser	Phe	His	Thr	Glu	Leu	His	Pro	Ara	Val	Δla		J J J
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Phe	Trp	Ile	Ile	Lys	Leu	Pro	Arg	Arg	Arg	Ser	His	Gln	Asp	Ala	Len		0.1
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gag	ggc	ggc	cac	tgg	ctc	anc	gar	aag	cqa	cac		cta	caq	acc	atc		689
Glu	Gly	Gly	His	Trp	Leu	Xaa	Glu	Lys	Arg	His	Ara	Leu	Gln	Ala	Ile		003
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Arg	Asp	Gly	Leu	Arg	Lys	Gly	Thr	His	Lys	Asp	Xaa	Leu	Xaa	Xaa	Glv		
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Thr	Glu	Ser	Ser	Ser	His	Ser	Arg	Leu	Ser	Pro	Arq	Lvs	Xaa	His	Leu		
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Leu	Tyr	Ile	Leu	Xaa	Pro	Ser	Arg	Gln	Leu	_			_				
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177



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												gta Val				105
												aga Arg -30				153
aar Lys	gca Ala -25	gct Ala	gjy aaa	cag Gln	atc Ile	cag Gln -20	gcc Ala	tgg Trp	tgg Trp	cgt Arg	999 Gly -15	gtc Val	ctg Leu	gtg Val	cgc Arg	201
agg Arg -10	acc Thr	ctg Leu	ctg Leu	gtt Val	gct Ala -5	gcc Ala	ctc Leu	agg Arg	gcc Ala	tgg Trp 1	atg Met	att Ile	cag Gln	tgc Cys 5	tgg Trp	249
												cgg Arg				297
												aag Lys 35				345
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cact	acco	ta a		tgto	t ga	ccag	gtaa	aaa	aaaa	aaa						583

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agg agc cat gct gac caa gac agc aac ccc aag gcg gaa gcc ctg ctc Arg Ser His Ala Asp Gln Asp Ser Asn Pro Lys Ala Glu Ala Leu Leu -25 -20 -15	321
ccc tgc aac ctg cac tgc agc tgg ctc cac agc agc ccc agg cca gat Pro Cys Asn Leu His Cys Ser Trp Leu His Ser Ser Pro Arg Pro Asp -10 -5 1 5	369
ccc cat tcc cac ttc cca tct ktc agg agg tgc cct ttg ccc cac cct Pro His Ser His Phe Pro Ser Xaa Arg Arg Cys Pro Leu Pro His Pro 10 15 20	417
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Lys Leu Asp Glu Lys Ala Pro Trp Asn Trp Phe Leu Ile Phe Ile Pro 1 5 10 15	
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•	
•	

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Ala Gly Ar	g Cys Lys	Ser Gly Phe	Asp Leu Asp	Met Asp His	Thr Ile	
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				tgtctttttt g		546
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Met	
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Ile Pro Leu Ile Ser His Leu Ala Glu Ala Ala Pro Pro Thr Ser Trp -30 -25 -20	
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Ser Leu Ile Ser Ser Val Leu Asn Val Gly His Leu Leu Phe Ser Ser	
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Ile Ile Leu Met Lys	
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                                        -15
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Gly Thr Arg Phe Lys Thr Ala Phe Gln Leu Leu Asp Phe Ile Leu Ala
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Val Leu Trp Ala Val Val Trp Phe Met Gly Phe Cys Phe Leu Ala Asn
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Gln Trp Gln His Ser Pro Pro Lys Glu Xaa Leu Leu Gly Ser Ser Ser
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Ile Pro Xaa Leu Pro Gly Xaa Pro Gly Pro Pro Lys
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Val														aaa Lys		453
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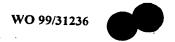
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cct cag gtc act ctc ctg gac ccc aat gaa aag Pro Gln Val Thr Leu Leu Asp Pro Asn Glu Lys 10 15 20	Tyr Leu Leu Arg Leu 25	199												
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ctg ccc acc gcc cac cac act ctg ggg ctg cct Leu Pro Thr Ala His His Thr Leu Gly Leu Pro 45 50	gtg ggc aaa cat atc Val Gly Lys His Ile 55	295												
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Pro Val Thr Ser Asp Glu Asp Gln Gly Tyr Val	gat ctt gtc mtc aag Asp Leu Val Xaa Lys 85	391												
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           Tyr Val Ser Tyr Leu Phe Ser Thr Asn Ser Pro Leu Ser Phe Arg Arg
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          Ile
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                                        Met Cys Leu Leu Thr Ala
tta gtt aca cag gtg att tcc tta aga aaa aat gca gag aga act tgt
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Leu Val Thr Gln Val Ile Ser Leu Arg Lys Asn Ala Glu Arg Thr Cys
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Ser Ser Thr Pro Cys Asp Ser Lys Phe Pro Thr Val Tyr Ser Ser Ala
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Pro Phe His Ala Pro Leu Pro Val Gln Asn Ser Leu Trp Gly His Pro
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ctc cat ggt tgt tcc tgg caa tgc cac cat ccc cag gga car aat ctc
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Leu His Gly Cys Ser Trp Gln Cys His His Pro Gln Gly Gln Asn Leu
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cag cct gcc agt ctc cad acc cat ctc tcc aag ccc aag cgc cat ttt
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Gln Pro Ala Ser Leu Xaa Thr His Leu Ser Lys Pro Lys Arg His Phe
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Xaa Lys Lys Xaa Cys Gln Ala
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-30
                    -25
                                       -20
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Glu Gly Ile Leu Ile Leu Trp Ile Ile Arg Leu Leu Phe Ser Lys Thr
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Tyr Lys Leu Gln Glu Arg Ser Asp Leu Thr Val Lys Glu Lys Glu Glu
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ctg att gaa gag tgg caa cca gaa cct ctt gtt cct cct gtc cca aaa
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Leu Ile Glu Glu Trp Gln Pro Glu Pro Leu Val Pro Pro Val Pro Lys
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gac cat cct gct ctc aac tac aac atc gtt tca ggc cct cca agc cac
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Asp His Pro Ala Leu Asn Tyr Asn Ile Val Ser Gly Pro Pro Ser His
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aaa act gtg gtg aat gga aaa gaa tgt ata aac ttc gcc tca ttt aat
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Lys Thr Val Val Asn Gly Lys Glu Cys Ile Asn Phe Ala Ser Phe Asn
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Phe Leu Gly Leu Leu Asp Asn Pro Arg Val Lys Ala Ala Ala Leu Ala
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Ser Leu Lys Lys Tyr Gly Val Gly Thr Cys Gly Pro Cys Gly Phe Tyr
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Gly Thr Phe Glu
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Val Asp Pro Gln Phe Leu Lys Leu Thr Lys Val Asp Asp Gln Ile Tyr	233
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tct gag ttc cgg aaa aat ttt gag acc ctt agg ata gat gtg ttg grc	292
Ser Glu Phe Arg Lys Asn Phe Glu Thr Leu Arg Ile Asp Val Leu Xaa	
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Glu Glu Lys Lys Glu Leu Thr Val Glu Lys Lys Arg Thr Pro Arg Met	
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Thr Lys Lys Ser Thr Lys Val Val Lys Lys Leu Cys Lys Val Tyr Arg	
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gctataattg atgatgatgt tcagataact gaagacacaa taa atg aca ttc aga	
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Met Thr Phe Arg	415
Met Thr Phe Arg -20	415
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ccc ctg cac ttt tct g Pro Leu His Phe Ser A -15	at cta att t sp Leu Ile S	Ser Val Leu	tac ctt ata Tyr Leu Ile	ccc aaa Pro Lys -5	210
aca ctt act acc aac a Thr Leu Thr Thr Asn T 1					258
atg mat ctg gta tta g Met Xaa Leu Val Leu G 15				agaaaaaga	311
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gcacacagac agacc atg ggg att ctg tct aca gtg aca gcc tta aca ttt  Met Gly Ile Leu Ser Thr Val Thr Ala Leu Thr Phe  -15  -10  -5	231
gcc aga gcc ctg gac ggc tgc aga aat ggc att gcc cac cct gca agt Ala Arg Ala Leu Asp Gly Cys Arg Asn Gly Ile Ala His Pro Ala Ser	279
gag aag cac aga ctc gag aaa tgt agg gaa ctc gag agc agc cac tcg Glu Lys His Arg Leu Glu Lys Cys Arg Glu Leu Glu Ser Ser His Ser 15 20 25	327
gcc cca gga tca acc cag cac cga aga aaa aca acc aga aga	375
tct tca gcc tgaaatgaak ccgggatcaa atggttgctg atcaragccc Ser Ser Ala	424
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Ser-Thr Gly Gln Leu Tyr Arg Met Glu Asp Ile Gly Arg Phe His Ser -55 -50 -45	
cag cag cca ggt tcc ctc acc cca agc tca ccc act gtt ggg gag att Gln Gln Pro Gly Ser Leu Thr Pro Ser Ser Pro Thr Val Gly Glu Ile -40 -35 -30	152
atc tac aat aac acc aga aac aca ttg ggg tgg att ggg ggt atc ctt  Ile Tyr Asn Asn Thr Arg Asn Thr Leu Gly Trp Ile Gly Gly Ile Leu -25 -10 -10	200
atg ggt tot ttt cag gga acc att gct gga caa ggc aca gga gcc acc Met Gly Ser Phe Gln Gly Thr Ile Ala Gly Gln Gly Thr Gly Ala Thr	248



-5 1 5 tec att tet gag ete tge aag gga eaa gaa eta gag eea tea ggg get	296
Ser Ile Ser Glu Leu Cys Lys Gly Gln Glu Leu Glu Pro Ser Gly Ala  10 15 20	296
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Gly Leu Thr Val Ala Pro Pro Gln Ala Val Ser Leu Gln Gly Ile Tyr 25 30 35	344
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Thr Leu Pro Trp Leu Leu Gln Leu Phe His Ser Thr Ala Leu Xaa Xaa 40 45 50 55	
dtt cag caa cct aat gga tct cta tct ctg aac atc tct tca tcc cat	440
Xaa Gln Gln Pro Asn Gly Ser Leu Ser Leu Asn Ile Ser Ser His  60 65 70	
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Ala Pro Xaa Pro Xaa Thr Cys Thr Leu Glu Pro Gly Val Asp Pro Thr 75 80 85	
cga sct gtc tgt att aat ccc cat ccc cca cca cca atc tta aaa abc	536
Arg Xaa Val Cys Ile Asn Pro His Pro Pro Pro Pro Ile Leu Lys Xaa 90 95 100	
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Pro Leu Ser Pro Tyr Pro Lys Pro Gln Leu Gly Thr His Ala Gly Gln 105 110 115	
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Val Asn	
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aggaacrtca ta atg rwn nnk ttc aca gac ccc tct tca gtg aat gaa aag	171
Met Xaa Xaa Phe Thr Asp Pro Ser Ser Val Asn Glu Lys	
-70 -65 -60	
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Lys Arg Arg Glu Arg Glu Arg Gln Asn Ile Val Leu Trp Arg Gln -55 -50 -45	
-55 -50 -45	

ccg ctc att acc ttg cag tat ttt tct ctg gaa atc ctt gta atc ttg



D۲	o Leu	Tle	Th r	T.e.11	Gln	Tur	Dhe	Ser	T. 211	Glu.	Tla	T 011	3701	T 3 A	Ton		
		-40					-35					-30					
	g gaa																315
Ly	s Glu	Trp	Thr	Ser	Lys	Leu	Trp	His	Arg	Gln	Ser	Ile	Val	Val	Ser		
	-25					-20					-15						
tt	t tta	ctg	ctg	ctt	gct	999	ctt	ata	gct	acg	tat	tat	gtt	gaa	gga		363
Ph	e Leu	Leu	Leu	Leu	Ala	Gly	Leu	Ile	Ala	Thr	Tyr	Tyr	Val	Glu	Gly		
-1	0				-5					1 .	_	-		5	-		
gt	g cat	caa	cag	tat	gtg	caa	cgt	ata	gag	aaa	cag	ttt	ctt	ttg	tat		411
Va	l His	Gln	Gln	Tyr	Val	Gln	Arg	Ile	Glu	Lys	Gln	Phe	Leu	Leu	Tyr	•	
			10			•		15					20		•		
gc	c tac	tgg	ata	ggc	tta	gga	att	ttg	tct	tct	gtt	999	ctt	gga	aca		459
Al	a Tyr	Trp	Ile	Gly	Leu	Gly	Ile	Leu	Ser	Ser	Val	Gly	Leu	Gly	Thr		
		25					30					35		_			
gg	g ctg	cac	acc	ttt	ctg	ctt	tat	ctg	ggt	cca	cat	ata	gcc	tca	gtt		507
Gl	y Leu	His	Thr	Phe	Leu	Leu	Tyr	Leu	Gly	Pro	His	Ile	Ala	Ser	Val		
	40		<u> </u>			45					50						
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Th	r Leu	Ala	Ala	Tyr	Glu	Cys	Asn	Ser	Val	Asn	Phe	Pro	Glu	Pro	Pro		
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ta	t cct	gat	cag	att	att	tgt	cca	gat	gaa	gag	ggc	act	gaa	gga	acc		603
Тy	r Pro	Asp	Gln	Ile	Ile	Cys	Pro	Asp	Glu	Glu	Gly	Thr	Glu	Gly	Thr		
				75		_		_	80					85			
at	t tct	ttg	tgg	agt	atc	atc	tca	aaa	gtt	agg	att	gaa	gcc	tgc	atg		651
Il	e Ser	Leu	Trp	Ser	Ile	Ile	Ser	Lys	Val	Arg	Ile	Glu	Ala	Cys	Met		
			90					95		_			100	-			
tg	g ggt	atc	ggt	aca	gca	atc	gga	gag	ctg	cct	cca	tat	ttc	atg	gcc		699
Tr	p Gly	Ile	Gly	Thr	Ala	Ile	Gly	Glu	Leu	Pro	Pro	Tyr	Phe	Met	Ala		
		105					110					115					
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Ar	g Ala	Ala	Arg	Leu	Ser	Gly	Ala	Glu	Pro	Asp	Asp	Glu	Glu	Tyr	Gln		
	120		-			125				_	130			•			
ga	a ttt	gaa	gag	atg	ctg	gaa	cat	gca	gag	tct	qca	caa	gta	aga	aca		795
Gl	ı Phe	Glu	Glu	Met	Leu	Glu	His	Ala	Glu	Ser	Āla	Gln	Val	Arg	Thr		
13					140					145				-	150		
gt	999	ata	gaa	aat	aga	aca	ctt	tac	ttc	ttc	cta	aag	agg	cta	tta		843
٧a.	lGly	Ile	Glu	Asn	Arg	Thr	Leu	Tyr	Phe	Phe	Leu	Lys	Arg	Leu	Leu		
				155				-	160			-	_	165			
ag	g taaa	aatto	gtt a	gtag	jttac	t ct	gaag	aaga	aaa	ctgo	taa	agta	aaaa		laaaa		901
Arg							- •					_					•

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_	_					_		_			_	_			aggaat	120
CCC	aaga	aga (	ctggg											gaa a		170
				1	Met (		Arg ( -35	Gln :	Ser .	Arg '		Met : -30	Ser	Glu 1	Lys	
gat	gag	tat	caq	ttt	caa			gga	aca	ata			ctt	gtc	ttc	218
														Val		
	-25		-			-20		2			-15					
aat	ttt	ttg	ctc	atc	ctt	acc	att	ttg	aca	atc	tgg	tta	ttt	aaa	aat	266
Asn	Phe	Leu	Leu	Ile	Leu	Thr	Ile	Leu	Thr	Ile	Trp	Leu	Phe	Lys	Asn	
-10		•			-5					1				5		
	_		_		_		_					_		tat		314
His	Arg	Phe	-	Phe	Leu	His	Glu		Gly	Gly	Ala	Met		Tyr	Gly	
			<b>\10</b>					15					20			
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ьeи	хаа		GIY	ьеп	TIE	Leu		ıyr	Ala	Thr	Ala		Tnr	Asp	TTE	
~~~	-a+	25	-at	~+ ~	<b>+</b> - +	~~~	30	~+ ~		a+	<del>-</del>	35	-~+		<b>t</b>	410
														cca Pro		410
Giu	40	Gry	Aud	Val	ıyı	45	Cys	٧٩٢	пуз	пец	50	FIIC	261	FIO	361	
act		cta	att	aat	atc		gac	caa	att	tat		tat	aaa	tac	aar	458
														Tyr		
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aga	gaa	ata	agt	cag	cac	amc	atc	aat	cct	cat	cam	gga	aat	gct	ata	506
														Ala		
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Leu	Glu	Lys		Thr	Phe	Asp	Pro		Ile	Phe	Phe	Asn	Val	Leu	Leu	
			90					95					100			
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PFO	Pro	11e	тте	Pne	HIS	ATA	_	Tyr	ser	Leu	ьуs	ьуs 115	Arg	His	Pne	
+++	caa		++=	~~ ·	+ c+	2++	110	200	+=+	~~~	++~		~~~	act	acc	650
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1110	120		<b>D</b> Cu	O <sub>1</sub> y	DCI	125	DC u	1111	- 7 -	Ala	130	ncu	OLY	1111	nau	
atc		tqc	atc	atc	ata		taa	gtga	cat '	tcaa		ca a	atta	caggi	t	701
			Ile				•				<b>.</b>					
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caa atg agc atg caa ttc ttg ttt aag atg gtg gcc tta tgc tgt tgt	168
Met Ser Met Gln Phe Leu Phe Lys Met Val Ala Leu Cys Cys	
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ctc tgg aag atc tcc ggc tgt gag gaa gtc cct cta act tac aac ctg	216
Leu Trp Lys Ile Ser Gly Cys Glu Glu Val Pro Leu Thr Tyr Asn Leu	
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Leu Lys Cys Leu Leu Asp Lys Ala His Cys Val Leu Leu Thr Pro Cys	
15 20 25	
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Gly Tyr Ile Phe Ser Leu Ile Ser Pro Glu Ile Leu Lys Leu Thr Leu	
30 35 40	
atc act ttg cav atc ctc tta ata ctc aaa aat cta cac tta ctg tgg	360
Ile Thr Leu Xaa Ile Leu Leu Ile Leu Lys Asn Leu His Leu Leu Trp	
45 50 55	
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Leu Thr Val Ser Ser Xaa Cys Val His Arg Ser Ser Ala Arg Lys Glu	
60 65 70	
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Lys	
75	
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tgtgaacatt caacattagg tttaaatttt atttttaaaa gttaataata aaaggatata	881
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180

240

300

360

410



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Leu Leu Leu His Phe Tyr Cys Leu Leu Arg Ser Ser Glu Tyr Ile Leu
-10 -5 1 5

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Gly Tyr Lys Val Leu Gly Val Phe Phe Pro Ile Leu

10

15

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Thr Tyr Cys Met Phe Gln Asp Lys Lys Tyr Arg Val Gly Glu Arg Trp
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cat cct tac ctg gaa cct tat ggg ttg gtt tac tgc gtg aac tgc atc
                                                                      309
His Pro Tyr Leu Glu Pro Tyr Gly Leu Val Tyr Cys Val Asn Cys Ile
                        30
tgc tca gag aat ggg aat gtg ctt tgc agc cga gtc aga tgt cca aat
                                                                      357
Cys Ser Glu Asn Gly Asn Val Leu Cys Ser Arg Val Arg Cys Pro Asn
                    45
                                        50
gtt cat tgc ctt tct cct gtg cat att cct cat ctg tgc tgc cct cgc
                                                                      405
Val His Cys Leu Ser Pro Val His Ile Pro His Leu Cys Cys Pro Arg
                60
                                    65
tgc cca gaa gac tcc tta ccc cca gtg aac aat rwg gtg acc agc
                                                                      450
Cys Pro Glu Asp Ser Leu Pro Pro Val Asn Asn Xaa Val Thr Ser
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Thr Leu Ile Ala Pro Arg Trp Leu Leu Thr Ala Ala His Cys Leu Lys	
35 40 45	
ccc cgc tac ata ktt cac ctg ggg cag cac aac ctc cag aag gag gag	359
Pro Arg Tyr Ile Xaa His Leu Gly Gln His Asn Leu Gln Lys Glu Glu	
50 55 60	
ggc tgt gag car acc cgg aca gcc act gag tcc ttc ccc cac ccc ggc	407
Gly Cys Glu Gln Thr Arg Thr Ala Thr Glu Ser Phe Pro His Pro Gly	
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Phe Asn Asn Ser Leu Pro Asn Lys Asp Xaa Xaa Asn Asp Ile Met Leu	
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gtg aak atg gma tcg cca gtc tcc atc acc tgg gct gtg cga ccc ctc	503
Val Xaa Met Xaa Ser Pro Val Ser Ile Thr Trp Ala Val Arg Pro Leu	
100 105 110	
acc ctc tcc tca cgc tgt gtc act gct ggc acc agc tgc ctc att tcc	551
Thr Leu Ser Ser Arg Cys Val Thr Ala Gly Thr Ser Cys Leu Ile Ser	
115 120 125	
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Gly Trp Gly Ser Thr Ser Ser Pro Gln Leu Arg Leu Pro His Thr Leu	
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Tyr Pro Gly Asn Ile Thr Asp Thr Met Val Cys Ala Ser Val Gln Glu 160 165 170 175	
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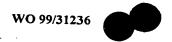
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Len Len His The Vol Low Com The Day between A get of Cot get	203
Leu Leu His Ile Val Leu Leu Ser Ile Pro Phe Val Ser Val Pro Val	
-5 1 5	
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35

15

30

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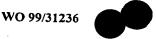
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tttg	gcago	tg o	cact	gago	t gt	agct	gcgt	aag	gtaco	tcc	ttga	tgc	etg t	cggc	cacttc	798
tgaa	aggo	cac a	aaggo	caac	ga ac	tcct	ggcd	agg	gacto	gcaa	ggct	ctg	cag d	ccaat	gcaga	858
aaat	gggt	ca ç	gctco	tttc	ga ga	acco	ctcc	cca	accta	ccc	cttc	ctto	cct o	ettta	atctct	918
CCC	catt	gt d	ttg	taaa	at at	agad	ttgg	, taa	attaa	aat	gttg	gatte	gaa g	gtctg	gaaaa	978
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gaagagetgt ggaggeeace etetacaaag etttatagaa ettetggate taacteacaa	
acaagettee agaagaget agagagetta germana telectigate taactcacaa	180
acaagettee agaagagact agagacetta ggccaggaga tgaaggagtt cagtagcaaa	240
gtcacacctg tccaattccc tgagctttgc tcactcagct a atg gga tgg caa agg Met Gly Trp Gln Arg -15	296
tgg tgg tgc ttt cat ctt cag gca gaa gcc tct gcc cat ccc cct caa	344
-10 -5 11 Pro Pro Gln	
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Gly Leu Gln Ala Gln Phe Ser Cys Cys Pro Trp Val Gly Ile Cys	303
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caggereary digeotract gerraagige ofgeaqqage egectgeeaa refreents	569
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tryattycct gragactitg gagccaaraa acactetgtg tgactetaca cacactteag	689
gradition of the same of the s	749
gaactaccat trataactic igitititta tigagaaaat gattcacgaa kkccaaatca	809
garrycodgg adgadatagg acgtgacggt actgggccct gtgattctcc cagcccttgc	869
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ryyyayadac cagagatggg aatgaggaaa atatgaacta cagcagaagc ccctgggcag	989
cigigalyga geoectgaca tracteteet tgeatetgte etgeettett teectetgee	1049
aggragegy graggatica gagigettag tetgeteact gggagaagaa gagiteetge	1109
geargeaage congonging agenging the tacathing and tototo tatototota	1169
categorial type that typical adalacetag categoriate tracectors	1229
described agadatigact egictetgia titigiatiaa geettaacae titigiaan	1289
regulation of decade attractions and accordance and accordance and accordance	1349
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seq LFLQLLVSHEIVC/AT

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gaa aag gcg taatgaaaac catcccgtcc ccattcctcc tcctctctga
                                                                     379
Glu Lys Ala
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ratttacacw wtgtattatg tattaacatg gcgtgtttat ttttgtattt ttctctggtt
                                                                     499
gggagtatka tatgaaggat caarateete aacteacaca tgtaracaaa cattasetet
                                                                     559
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aaagatcaga ggacctacag agagggctct ttggtttgag gaccatggct tacctttcct
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Met Glu His Tyr Arg Lys Ala Gly Ser Val Glu Leu Pro Ala	
-50 -45 -40	
cet tee eea atg eee eag eta eet eet gat ace ett gag atg egg gte	158
Pro Ser Pro Met Pro Gln Leu Pro Pro Asp Thr Leu Glu Met Arg Val	
-35 -30 -25	
cga gat ggc agc aaa att cgc aac ctg ctg ggg ttg gct ctg ggt cgg	206
Arg Asp Gly Ser Lys Ile Arg Asn Leu Leu Gly Leu Ala Leu Gly Arg	
-20 -15 -10	
ttg gag ggc ggc agt gct cgg cat gta gtg ttc tca ggt tct ggc agg	254



•																	-
	-5					1				5				Gly	1.0		
Ala	Ala	GIŷ	Lys	Ala 15	Val	Ser	Cys	Ala	Glu 20	Ile	Val	Lys	Arg	cgg Arg 25	Val	•	302
Pro	GIY	Leu	His 30	Gln	Leu	Thr	Lys	Leu 35	Xaa	Phe	Leu	Gln	Thr	gag Glu	Asp	:	350
ser	Trp	Val 45	Pro	Xaa	Ser	Pro	Asp 50	Thr	Gly	Leu	Xaa	Pro 55	Leu	aca Thr	Val	3	398
Arg	Arg 60	HIS	vaı	Pro	Ala	Xaa 65	Trp	Val	Leu	Leu	Xaa 70	Arg	Asp	ccc Pro	Leu	4	46
Asp 75	Pro	Asn	Glu	Cys	Gly 80	Tyr	Gln	Pro	Pro	Gly 85	Ala	Pro	Pro	ggc Gly	Leu 90	4	94
GIY	ser	Met	Pro	Ser 95	Ser	Ser	Cys	Gly	Pro 100	Arg	Ser	Xaa	Lys	agg Arg 105	Ala	5	42
cra Xaa	rac Xaa	Inr	cga Arg 110	tcg Ser	tgaa	aacc	tg c	tgas	ccag	c ct	gtto	tccg	ggc	ctra	atg	5	97
tctg	gggt	gc t	tgtg	cctt	t tc	tran	aago	gtt	gtga	skg	ctca	acat	cc c	cato	aaggt	6	57
ttga	grcc	ac a	aaag	tgga	c ct	ccct	atca	tgc	ttcc	cct	tece	tota	ac a	tata	adaad	7	17
ggac	tgct	gt g	aaga	atga	c ag	atgt	gggg	cct	ctac	caa	atto	toca	tt a	ctaa	ataad	7	77
ggct	CCCE	ct g	CCLE	ctac	c ta	cagt	gcat	ttg	aact	acc	ttct	gaaa	ga g	gtcc	akgga	8	37
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Leu His Cys	Phe Pro As	sp Leu Pro 1	Thr Glu Met	Pro Leu Xaa	a Ala Lys	
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ascaatcttt	tttctgttca	cggtgtttgt	gataaaacct	taaattccgc	aagcatcagt	545
			wwacaggcaa			605
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	Met His His G. -50	ly Leu Thr Pro	Leu Leu Leu Gly							
gta cat gag caa aaa				158						
Val His Glu Gln Lys				150						
-35		-30	-25							
gca aat tta aat gca				206						
Ala Asn Leu Asn Ala										
-20		-15	-10							
gct gta tgt tgt gga				254						
Ala Val Cys Cys Gly	Ser Ala Ser	_	u Leu Leu Glu Gln							
-5	1									
aac att gat gta tct				302						
Asn Ile Asp Val Ser			=							
	15	20	25							
tat gct gtt tct agt	cgt cat aat	gta att tgc ca	g tta ctt tct gac	350						
Tyr Ala Val Ser Ser	Arg His Asn									
30		35	40							
tac aaa raa aaa cag				398						
Tyr Lys Xaa Lys Gln 45		val Ser Ser Gl 50	u Asn Ser Asn Pro							
	-									
raa caa gac tta aag				146						
Xaa Gln Asp Leu Lys	65	Giu Giu Giu se	70							
gga agt gaa aat agc		gaa atg tct ca	• •	194						
Gly Ser Glu Asn Ser	Gln Pro Glu	Glu Met Ser Gl	n Glu Pro Glu Ile							
75	80	85								



aat arg ggt ggt gat aga aag gtt gaa raa raa atg aar aag cac gg	a 542
Asn Xaa Gly Gly Asp Arg Lys Val Glu Xaa Xaa Met Lys Lys His Gl 90 95 100 10	5
agt wet cat atg gga tte eea raa aac etg met aac ggt gee aet ge	± 590
Ser Xaa His Met Gly Phe Pro Xaa Asn Leu Xaa Asn Gly Ala Thr Al. 110 115 120	a
gac aat ggt gat gat gga tta att ccm cca rgg aaa asc ara aca cc	t 638
Asp Asn Gly Asp Asp Gly Leu Ile Pro Pro Xaa Lys Xaa Xaa Thr Pro 125 130 135	
gaa age cas caa ttt cet gae act gag aat gaa cag tat cac agg gae	c 686
Glu Ser Xaa Gln Phe Pro Asp Thr Glu Asn Glu Gln Tyr His Arg Asp	<u>p</u>
ttt tot gge cat ecc mae ttt ecc acd acc ett ecc atc aaa cag	
Phe Ser Gly His Pro Xaa Phe Pro Thr Thr Leu Pro Ile Lys Gln	731
155 160 165	
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Val Ile Ala Asp Thr Asp Glu Met Ser Ala Asn Lys Ile Asn Ser Phe

170



PCT

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gaa d	cta	rat	cga	gsk	gat	aga	rac	cct	agt	aac		twt	acc	aaa	tac	345
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70					75					8.0					85	
tac a	att	cac	cga	att	cca	ara	agc	cgg	gag	gtt	cag	cag	tcc	tgg	CCC	393
Tyr I	Ile	His	Arg		Pro	Xaa	Ser	Arg	Glu	Val	Gln	Gln	Ser	Trp	Pro	
				90					95					100		
tcc a	acc rh~	gtt	tyc	acc	acc	ttg	cac	tcc	atg	tgg	ctc	tcc	ttk	CCC	cta	441
Ser 1	LIIL	vaı	105	Inr	Inr	Leu	HIS		Met	Trp	Leu	Ser		Pro	Leu	
att c	cac	agg		aac	CCa	rat	++~	110	++~	+~+	224	~~~	115			400
Ile H	lis	Ara	Val	Lvs	Pro	Xaa	Leu	Val	Len	Cve	Acn	Gly	Dro	Gly	aca Th~	489
		120		-1-		••••	125	• • • •	J.C.u	Cys	ASII	130	FIU	GIY	TIII	
tgt g	gty	cct	atc	tgt	gta	tct		ctt	ctc	ctt	aaa		cta	ασа	ata	537
Cys V	/al	Pro	Ile	Cys	Val	Ser	Āla	Leu	Leu	Leu	Gly	Ile	Leu	Glv	Ile	55,
1	135					140					145					
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Lys I	ъys	Val	Ile	Ile		Tyr	Val	Glu	Ser	Ile	Cys	Arg	Val	Lys	Thr	
150					155					160					165	
tta t	cc	atg	tcc	gga	aag	att	ctg	ttt	cat	ctc	tca	aat	tac	ttc	att	633
Leu S	er	Met	Ser		Lys	lle	Leu	Phe		Leu	Ser	Asn	Tyr		Ile	
att c	יםת	taa	cca	170	ata				175					180		
gtt c	ln	Tro	Pro	MI	Len	Live	Glu	Lvc	Tire	DTO	aaa	ccg	gtg	tac	ctt	681
			185		DCu	בעם	Giu	190	TYL	PIO	БУБ	ser	195	Tyr	Leu	
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Gly A	rg	Ile	Val	_				_			,		,			,,,,
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-15

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1111	Бец	19F	ıyr	ьуs	Leu	Ala	Val 20	Glu	Gln	Leu	Gln	arc Xaa 25	cat His	Pro	Glu	266	5
AIG	30	GIU	Ата	Leu	GIY	Pro 35	Pro	Leu	Asn	Ile	His	tat Tyr	Leu	Lys	Leu	314	:
atc Ile 45	gac Asp	agg Arg	gaa Glu	aac Asn	ttc Phe 50	gtg Val	gac Asp	att Ile	gtt Val	Xaa	gcc Ala	aag Lys	ttg Leu	aaa Lys	att Ile	362	
cct Pro	vai	sei	GIY	Ser 65	aaa Lys	ser	Glu	Gly	Leu 70	Leu	Tyr	gtc Val	His	Ser	Ser	410	
Arg	GIY	GTA'	80	Pne	GIn	Arg	Trp	His 85	Leu	Asp	Glu	gtc Val	Phe	Leu	Glu	458	
Dea	пуs	95	GIY	Gin	GIn	Ile	Pro 100	Val	Phe	Lys	Leu	agt Ser 105	Gly	Glu	Asn	506	
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~~5	caac	LL L	99 - 9	Lddi	t ct	aact	taaa	cac	aaca	aat .	act a	+++~	+			737	
tgta	taaa	aa a	gcac	atga	t ac	aagg	aatt	taa aaa	gata	atg	taat	gtat	tt g	aaag	tgctt tttaa	797	
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aca Thr			ctg					aaa					gar			302
cat His		aga				tgag		etg (	cagaa	aagaa	aa ti		cgcca	a		350
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gag ' Glu ' 1	Tyr	Thr	Trp	Glu 5	Val	Phe	Gly	Tyr	Cys 10	Gln	Glu	Leu	Glu	Leu 15	Ser	207
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	Glu 50	Leu	Leu	Phe	Leu	His 55	Val	Tyr	Glu	Phe	Asp 60	Glu	Xaa	Met	Phe	351
Pro :	Lys	Asn	Val	Arg	Cys 70	Ser	Thr	Cys	Asp	Leu 75	Arg	Lys	Pro	Ala	Arg 80	399
tcc : Ser :	aas Xaa	cac His	tgc Cys	akt Xaa 85	gtg Val	tgt Cys	aac Asn	tgg Trp	tgt Cys 90	gtg Val	cac His	cgt Arg	ttc Phe	rac Xaa 95	cat His	447





cac	tgt	gtt	tgg	gtg	aac	aac	tgc	atc	999	gcc	tgg	aac	atc	agg	tmc		495
His	Cys	Val	Trp	Val	Asn	Asn	Cys		Gly	Ala	Trp	Asn	Ile	Arg	Xaa		
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Phe	Leu	Ile	Tyr	Val	Leu	Thr	Leu	Thr	Ala	Ser	Ala	Ala	Thr	Val	Āla		
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Gly	Leu	Arg	Xaa	Asn	Leu	Gln	Glu	Ile	Phe	Leu	Pro	Ala	Phe	Pro	Cvs		
_		_		245					250					255	C <sub>I</sub> C		
cat	gag	agg	aaq	aaa	caa	qaa	tgac	magt		tgac	tacc	:+ ++	gagg				978
His	Glu	Arg	Lys	Lvs	Gln	Glu			. J		-550		-5-5-	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	•		,,,
		_	260	4													
gtto	ccgt	tt a	ttta	caca	it at	ggat	cata	ath	ttac	aaa	2222		22			7.	028
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654

702

750



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gtg cct gga gcc agt c Val Pro Gly Ala Ser F	cc acc ac		g ttt	cct cct			254
aca ggt ccc ave acc g Thr Gly Pro Xaa Thr A	at ggc at		t gcc		tct gca		302
ggt ccc ttt tgt gct t Gly Pro Phe Cys Ala S 25		ro Ser Gl					350
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ggagttattt aaacattgca	taactact	tta atati	ataaa	gcaatat	tgc atca	tattat	420
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Met Leu Xaa Leu Ser Arg Ala Thr Lys

BNSDOCID: <WO 9931236A2>





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Arg Pro Ser Met Ala Ala Ser Gly Thr Ser Trp Ile Ser Ser Thr Leu
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Ala His Ser Leu Ser Leu Arg Asp Val Ser Glu Arg Leu Cys Ser Cys
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Ser Ser Gly Val His Arg Lys Ser Ser Arg Leu Phe Tyr Ile Arg Thr
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                                        60
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Pro Met Arg Arg Ser Ser Cys His Leu Xaa Cys Gln Val Ile Phe Leu
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                                                       Met Ser
 ctg act tcc agt tcc agc gta cga gtt gaa tgg atc gca gca gtt acc
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                     15
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 Lys Asp Asn Pro Lys Ile Val His Ala Phe Asp Met Glu Asp Leu Gly
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                                                                     404
 Cys Asp Gly Ala His Thr Lys His Asn Glu Glu Thr Gly Asp Asn Val
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                                                70
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 Gly Pro Leu Ile Ile Lys Lys Lys Glu Thr
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1 5 10													
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80 85 90													
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Ile Ile Asp Asn Arg Asp Phe Pro Xaa Asp Pro Gly Met Gln Trp Asp													
95 100 105													
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125 130 135 140													
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His	Arg	Xaa	Ile	Lys	Gly	Gln	Asn	Val	Leu	Leu	Thr	Glu	Asn	Ala	Glu	
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Val	Lys	Leu	Val	Asp	Phe	Gly	Xaa	Xaa	Ala	Gln	Leu	Asp	Arg	Thr	Val	
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Gly	Arg	Xaa	Asn	Thr	Phe	Ile	Gly	Thr	Pro	Tyr	Trp	Met	Ala	Pro	Xaa	
				75					80					85		
gtt	att	gcc	tgt	gat	gaa	aac	cca	sat	gcc	aca	tat	gat	ttc	aar	art	540
Val	Ile	Ala	Cys	Asp	Glu	Asn	Pro	Xaa	Ala	Thr	Tyr	Asp	Phe	Lys	Xaa	
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gac	ttg	tgg	tct	ttg	ggt	atc	acc	gcc	att	gaa	atg	gca	gaa	ggg	ctc	588
Asp	Leu	Trp	Ser	Leu	Gly	Ile	Thr	Ala	Ile	Glu	Met	Ala	Glu	Gly	Leu	
		105					110					115				
CCC	ctc	tct	gtg	aca	tgc	acc	cca	tgag	gagct	ct d	ttcc	ctcat	cc cc	ccgg	gaatc	642
Pro	Leu	Ser	Val	Thr	Cys	Thr	Pro									
	120					125										
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gctt	ggta	aaa a	aaato	cacag	ge <b>c</b> a	agcga	accag	g caa	acaga	aaca	atte	gatga	aag	catco	cattta	762
tace	gagad	ca	accta	aatga	ag cg	gaca	gtc	gca	attca	aact	caag	ggac	cat a	attga	atagaa	822
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Leu Trp Arg Gly Arg Ile Pro Gly Arg Gln Trp Ile Gly Lys His Arg -5 1 5	
cgg ccg cgg ttc gtg tcg ttg cgc gcc aag cag aac atg atc cgc cgc	152
Arg Pro Arg Phe Val Ser Leu Arg Ala Lys Gln Asn Met Ile Arg Arg 10 15 20	
ctg gag atc gag gcg gag aac cat tac tgg ctg agc atg ccc tac atg	200
Leu Glu Ile Glu Ala Glu Asn His Tyr Trp Leu Ser Met Pro Tyr Met  25 30 35 40	
acc cgg gag cag gag cgc ggc cac gcc gcg ttg cgc agg agg gag gcc	248
Thr Arg Giu Gin Glu Arg Gly His Ala Ala Leu Arg Arg Arg Glu Ala 45 50 55	
ttc gag gcc ata aag gcg gcc gcc act tcc aag ttc ccc ccg cat aga	296
Phe Glu Ala Ile Lys Ala Ala Ala Thr Ser Lys Phe Pro Pro His Arg 60 65 70	
ttc att gcg gac cag ctc gac cat ctc aat vgt cac caa gaa atg gtc	344
Phe lie Ala Asp Gin Leu Asp His Leu Asn Xaa His Gln Glu Met Val 75 80 85	
cta atc ctg agt cgt cac cct tgg att tta tgg atc acg gag ctg acc	392
Leu lie Leu Ser Arg His Pro Trp Ile Leu Trp Ile Thr Glu Leu Thr 90 95 100	
atc ttt acc tgg tct gga ctg aaa aac tgt agc ttg tgt gaa aat gag	440
The Phe Thr Trp Ser Gly Leu Lys Asn Cys Ser Leu Cys Glu Asn Glu	
110 115 120	
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Leu Trp Thr Ser Leu Tyr 125	
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<213> Homo sapiens

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<222> 9..185

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<222> 9..50

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<221> polyA\_site

<222> 906..918

<400> 369

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			ctg Leu 20													146
_			cat His	_		_	_	-	_				tgaa	aaggo	cca	195
actt	cgaa		aaag	tgaa	a go	gaga	cktt	t.ac	aara	acra	kttc		ac t	atca	acagga	255
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_									-			_			aaktca	
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<222> 442..447

<221> polyA\_site <222> 458..471

<400> 370

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												tat Tyr 5				145
												tcc Ser				193
atc Ile 25	ctc Leu	ttc Pbe	tgc Cys	aac Asn	tac Tyr 30	tat Tyr	gtt Val	tta Leu	ttt Phe	aaa Lys 35	ctt Leu	ctc Leu	cgg Arg	gac Asp	aga Arg 40	241



wta kta tta ggc agg gca tac tcc tac cca ctc aac agt tat gaa ctc Xaa Xaa Leu Gly Arg Ala Tyr Ser Tyr Pro Leu Asn Ser Tyr Glu Leu 45 50 55	289
aag gca aac twa gct gcc tct caw caa tgagggagaa ctcagataaa Lys Ala Asn Xaa Ala Ala Ser Xaa Gln 60 65	336
aatattttca tacgttctat ttttttcttg tgatttttat aaatatttaa gatattttat attttgtata ctattatgtt ttgaaagtcg ggaagagtaa gggatattaa atgtatccgt aaacaaaaaa aaaaam	396 456 472
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ggc ctg gcc ctc tgc aag cgg ctg ctg gcg gaa gat gat gag ctt cat Gly Leu Ala Leu Cys Lys Arg Leu Leu Ala Glu Asp Asp Glu Leu His -40 -35 -30	159
ctg tgt ttg gcg tgc agg aat atg agc aag gca gaa gct gtc tgt gct Leu Cys Leu Ala Cys Arg Asn Met Ser Lys Ala Glu Ala Val Cys Ala -25 -20 -15 -10	207
get etg etg gee tet eac eec act get gag gte acc att gte cag gro	255



gtc Val	ttt Phe	ggc Gly 90	cat His	ttt Phe	atc Ile	ctg Leu	att Ile 95	cgg Arg	gaa Glu	ctg Leu	gag Glu	cct Pro 100	ctc Leu	ctc Leu	tgt Cys	543
His	Ser 105	Asp	aat Asn	Pro	Ser	Gln 110	Leu	Ile	Trp	Thr	Ser 115	Ser	Arg	Ser	Ala	591
Arg 120	Lys	Ser	aat Asn	Phe	Ser 125	Leu	Glu	Asp	Phe	Gln 130	His	Ser	Lys	Gly	Lys 135	639
gaa Glu	Pro	tac Tyr	agc Ser	tct Ser 140	tcc Ser	aaa Lys	tat Tyr	gcc Ala	act Thr 145	gac Asp	ctt Leu	ttg Leu	agt Ser	gtg Val 150	gct Ala	687
Leu	Asn	Arg	aac Asn 155	Phe	Asn	Gln	Gln	Gly 160	Leu	Tyr	Ser	Asn	Val 165	Ala	Cys	735
Pro	Gly	Thr 170	gca .Ala	Leu	Thr	Asn	Leu 175	Thr	Tyr	Gly	Ile	Leu 180	Pro	Pro	Phe	783
Ile	Trp 185	Thr	ctg Leu	Leu	Met	Pro 190	Ala	Ile	Leu	Leu	Leu 195	Arg	Phe	Phe	Ala	831
Asn 200	Ala	Phe	act Thr	Leu	Thr 205	Pro	Tyr	Asn	Gly	Thr 210	Glu	Āla	Leu	Val	Trp 215	879
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			act Thr 235													975
			gaa Glu													1023
			cac His													1071
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<213> Homo sapiens

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<221> CDS

<222> 274..597

<221> sig\_peptide <222> 274..399

<223> Von Heijne matrix score 5.19999980926514

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seq VLCTNQVLITARA/VP





<222> 1027..1040

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Ile Ser Ser Pro Leu Val Glu Phe Val Lys Val Leu Cys Thr Asn Gln  -20  gtt ctc att act gcc agg gct gtg cct aca aaa aag gca tct gtg cga  Val Leu Ile Thr Ala Arg Ala Val Pro Thr Lys Lys Ala Ser Val Arg  -5  tgt gtg gaa aaa agg ttt tgg ata cca aaa act aca agc aaa cat ctg  Gys Val Glu Lys Arg Phe Trp Ile Pro Lys Thr Thr Ser Lys His Leu  10  15  20  25  tct aga tgt att gat gga att tct ggc ttt cta aat gat ttt act ttc  Asp Gly Ile Ser Gly Phe Leu Asn Asp Phe Thr Phe  30  35  40  tgc ctt gaa ttt tca agg cat aga tgt caa ctt aca gaa taacatgtkt  479  Cys Leu Glu Phe Ser Arg His Arg Cys Gln Leu Thr Glu  45  taagataatt aagtktaaac cagaraattt gattgttact cattttgctc tcatgtkcta  aaacagcaac agtgtaacta gtctttgtt gtaaatggt attttcctta taaaaatttt  599  taagataatta taagtktaaac caccacct ttatttataa atactgcaa aktgaraagg  719  agataataaa tacttgctc tgaatttgc atccaagtt accattcc ccccaccac  cttgctggtg tcatagtat tagaatcag agcctctaa accattgcg tttcatagga  tatataaaatg tttcaagcca ttattgctg atcgttcttt  tgattgttct ttggccaaataac ctagaccaca  agtgtaataaa tacttgccc atcaagca agcctcttaa gtcaattaac ctagaccaa  atcaaagacc agttggattt atgatattt ttatttgttc ttgcagccaa agtgccagtt  559  tctttaatat gtgaccaaga accacagga catccatat gccaatat gtcaataa ttgaccaa agtgccagtt  599  tctttaatat gtgaccaaga accacagga catccatat gccaatata ttgaccaa agtgccaat  599  tctttaatat gtgaccaaga accacagga catccatat gccaaataa tacactgaa agtgccagtt  599	<del></del>	
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gtt ctc att act gcc agg gct gtg cct aca aaa aag gca tct gtg cga Val Leu Ile Thr Ala Arg Ala Val Pro Thr Lys Lys Ala Ser Val Arg -5 1 5  tgt gtg gaa aaa agg ttt tgg ata cca aaa act aca agc aaa cat ctg 382 Cys Val Glu Lys Arg Phe Trp Ile Pro Lys Thr Thr Ser Lys His Leu 10 15 20 25  tct aga tgt att gat gga att tct ggc ttt cta aat gat ttt act ttc 430 Ser Arg Cys Ile Asp Gly Ile Ser Gly Phe Leu Asn Asp Phe Thr Phe 30 35 40  tgc ctt gaa ttt tca agg cat aga tgt caa ctt aca gaa taacatgtkt 479 Cys Leu Glu Phe Ser Arg His Arg Cys Gln Leu Thr Glu 45 taagataatt aagtktaaac cagaraattt gattgttact cattttgctc tcatgtkcta 539 aaacagcaac agtgtaacta gtcttttgtt gtaaatggt attttcctta taaaaaattt 599 aaaaactaag tggcaaattc catgaaaata tttctcagtt ctgtatgcac ttttattaa 659 cattattcat ataattccc ccccaccact ttatttat		
Val Leu Ile Thr Ala Arg Ala Val Pro Thr Lys Lys Ala Ser Val Arg  -5		224
tgt gtg gaa aaa agg ttt tgg ata cca aaa act aca agc aaa cat ctg 382 Cys Val Glu Lys Arg Phe Trp Ile Pro Lys Thr Thr Ser Lys His Leu 10 15 20 25  tct aga tgt att gat gga att tct ggc ttt cta aat gat ttt act ttc 430 Ser Arg Cys Ile Asp Gly Ile Ser Gly Phe Leu Asn Asp Phe Thr Phe 30 35 40  tgc ctt gaa ttt tca agg cat aga tgt caa ctt aca gaa taacatgtkt 479 Cys Leu Glu Phe Ser Arg His Arg Cys Gln Leu Thr Glu 45 50  taagataatt aagtktaaac cagaraattt gattgttact cattttgctc tcatgtkcta 539 aaacagcaac agtgtaacta gtctttgtt gtaaatggtt attttcctta taaaaattt 599 aaaaactaag tggcaaattc catgaaata tttctcagtt ctgtatgcac ttttattaa 659 cattattcat ataattctcc ccccaccact ttatttat	Val Leu Tle Thr Ala Arg Ala Val Dro Thr Lug Ala Com Val Arg	334
tgt gtg gaa aaa agg ttt tgg ata cca aaa act aca agc aaa cat ctg Cys Val Glu Lys Arg Phe Trp Ile Pro Lys Thr Thr Ser Lys His Leu 10 15 20 25  tct aga tgt att gat gga att tct ggc ttt cta aat gat ttt act ttc 430 Ser Arg Cys Ile Asp Gly Ile Ser Gly Phe Leu Asn Asp Phe Thr Phe 30 35 40  tgc ctt gaa ttt tca agg cat aga tgt caa ctt aca gaa taacatgtkt 479 Cys Leu Glu Phe Ser Arg His Arg Cys Gln Leu Thr Glu 45 50  taagataatt aagtktaaac cagaraattt gattgttact cattttgctc tcatgtkcta aaacagcaac agtgtaacta gtcttttgtt gtaaatggtt attttcctta taaaaatttt 599 aaaaactaag tggcaaattc catgaaaata tttctcagtt ctgtatgcac ttttattaa 659 cattattcat ataattctcc ccccaccact ttatttat		
Cys Val Glu Lys Arg Phe Trp Ile Pro Lys Thr Thr Ser Lys His Leu  10 15 20 25  tct aga tgt att gat gga att tct ggc ttt cta aat gat ttt act ttc 430  Ser Arg Cys Ile Asp Gly Ile Ser Gly Phe Leu Asn Asp Phe Thr Phe  30 35 40  tgc ctt gaa ttt tca agg cat aga tgt caa ctt aca gaa taacatgtkt 479  Cys Leu Glu Phe Ser Arg His Arg Cys Gln Leu Thr Glu  45 50  taagataatt aagtktaaac cagaraattt gattgttact cattttgctc tcatgtkcta 539  aaacagcaac agtgtaacta gtcttttgtt gtaaatggtt attttcctta taaaaatttt 599  aaaaactaag tggcaaattc catgaaaata tttctcagtt ctgtatgcac ttttattaa 659  cattattcat ataattctcc ccccaccact ttatttat		382
10 15 20 25  tct aga tgt att gat gga att tct ggc ttt cta aat gat ttt act ttc 430  Ser Arg Cys Ile Asp Gly Ile Ser Gly Phe Leu Asn Asp Phe Thr Phe  30 35 40  tgc ctt gaa ttt tca agg cat aga tgt caa ctt aca gaa taacatgtkt 479  Cys Leu Glu Phe Ser Arg His Arg Cys Gln Leu Thr Glu  45 50  taagataatt aagtktaaac cagaraattt gattgttact cattttgctc tcatgtkcta 539  aaacagcaac agtgtaacta gtcttttgtt gtaaatggtt attttcctta taaaaatttt 599  aaaaactaag tggcaaattc catgaaaata tttctcagtt ctgtatgcac ttttattaa 659  cattattcat ataattctcc ccccaccact ttatttat		302
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Cys Leu Glu Phe Ser Arg His Arg Cys Gln Leu Thr Glu  45 50  taagataatt aagtktaaac cagaraattt gattgttact cattttgctc tcatgtkcta 539 aaacagcaac agtgtaacta gtcttttgtt gtaaatggtt attttcctta taaaaatttt 599 aaaaactaag tggcaaattc catgaaaata tttctcagtt ctgtatgcac ttttatttaa 659 cattattcat ataattctcc ccccaccact ttatttat		
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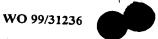
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-40

-35

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Glu Cys Ile Asp Trp Ser Glu Arg Arg Asn Ala Val Ala Ser Val Val



		-30					-25					-20						
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	Ala	Gly	Ile	Leu	Phe	Phe	Thr	Gly	Trp	Trp	Ile	Met	Ile	Asp	Āla	Ala		
	-15					-10					-5					1		
	gtg	gtg	tat	cct	aag	cca	gaa	cag	ttg	aac	cat	gcc	ttt	cac	aca	tgt		254
	vaı	vai	Tyr	Pro	Lys	Pro	Glu	Gln	Leu	Asn	His	Ala	Phe	His	Thr	Cys		
	aat	~+ ·		5		<b></b>			10					15				
	Glv	Val	Dhe	Coc	aca Th~	ttg	gct	TTC	ttc	atg	ata	aat	gct	gta	tcc	aat		302
	Gry	vai	20	Ser	1111	Leu	ATA	Pne 25	Pne	Met	He	Asn		Val	Ser	Asn		
	act	caq		aga	aat	nat	200		~~~	200			30					
	Ala	Gln	Val	-Ara-	-Glv	gat Asp	Ser	Tyr	gaa Glu	age -cor-	990	-Crro-	tta Tan-	gga	aga	aca -mb		350
		35		9	,	21010	40	- y -	Giu	SET	GIY	45	Leu	GIY	Arg	THE		
	ggt	gct	cqa	qtt	taa	ctt		att	aat.	ttc	ato		ato	+++	~~~	tas		398
	Gly	Āla	Arg	Val	Trp	Leu	Phe	Ile	Glv	Phe	Met	Len	Met	Dhe	999	Ser		370
	50		_		•	55			1		60			1 110	Oly	65		
	ctt	att	gct	tcc	atg	tgg	att	ctt	ttt	ggt	gca	tat	qtt	acc	caa	aat		446
	Leu	Ile	Ala	Ser	Met	$\mathtt{Trp}$	Ile	Leu	Phe	Gly	Ala	Tyr	Val	Thr	Gln	Asn		
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	act	gat	gtt	tat	ccg	gga	cta	gct	gtg	ttt	ttt	caa	aat	gca	ctt	ata	4	494
	Thr	Asp	Val	Tyr	Pro	Gly	Leu	Ala	Val	Phe	Phe	Gln	Asn	Ala	Leu	Ile		
				85					90					95				
	שמ	בננ	agc	act	ctg	atc	tac	aaa	ttt	gga	aga	acc	gaa	gag	cta	tgg	5	542
	Pne	Pne	ser	Inr	Leu	Ile	Tyr	Lys	Phe	Gly	Arg			Glu	Leu	Trp		
	200	tasa	100	a+ +				105					110					
	Thr					agto												595
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	tgtt	CCCC	ta c	attt	ttat	g tt	ctga	gttt	tga	aata	att	ttat	gaaa	tt t	cttt	atttt	7	715
	tcat	rgca	ta g	actg	ttaa	t at	gtat	ataa	tac	aaga	cta	tata	aatt	aa a	taat	gagta	7	775
	ccag		tt a	ttcc	tgag	a tt	taga	actt	gat	ctac	tcc	ctga	gcca	gg g	ttac	atcat	8	335
	taat	ccat	ככ כ	agaa	gtaa	c ca	ctct	tgtc	tct	ctgg	ctg	ggca	cggt	gg c	tcat	gcctg	8	395
	caal	ctca	gc a	CTET	ggga 	g gc	cgag	gcgg	gcc	gatt	gct	tgag	gtca	ag t	gttt	gagac	9	955
1	tagt	ccgg	oc a	tata	ggcg	a aa	cccc	atct	act	aaaa	ata	caaa	aatt	ag c	cagg	catgg	10	15
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	ataa.	3354 aact	20 2	tete	yayı əəən	g ag a aa	olya	gttt ama	gcg	ccac	tgc	actc	tagc	ct g	9999	agaaa		.35
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														gtg Val 25		197
gtg Val	act Thr	gga Gly	gcc Ala 30	tcg Ser	agt Ser	gga Gly	att Ile	ggt Gly 35	gag Glu	gag Glu	ctg Leu	gct Ala	tac Tyr 40	cag Gln	ttg Leu	245
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947



<221> polyA\_site <222> 937..947

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<sup>&</sup>lt;220>

<sup>&</sup>lt;221> CDS

<sup>&</sup>lt;222> 46..585

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Leu Ser Arg Ala Asn Ser Leu Phe Ala Phe Ser Leu Ser Val Met A -20 -15 -10	A1a
gcg ctc acc ttc ggc tgc ttc atc ayy acc gcc ttc aaa gac agg a	agc 153
Ala Leu Thr Phe Gly Cys Phe Ile Xaa Thr Ala Phe Lys Asp Arg S -5 1 10	ser
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Val Pro Val Arg Leu His Val Ser Arg Ile Met Leu Lys Asn Val G 15 20 25	3lu
gat ttc act gga cct aga gaa aga agt gat ctg gga ttt atc aca t	tt . 249
Asp Phe Thr Gly Pro Arg Glu Arg Ser Asp Leu Gly Phe Ile Thr Pi	Phe
gat ata act gct gat cta gag aat ata ttt gat tgg aat gtt aag c	ag 297
Asp Ile Thr Ala Asp Leu Glu Asn Ile Phe Asp Trp Asn Val Lys G 45 50 55	
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Leu Phe Leu Tyr Leu Ser Ala Glu Tyr Ser Thr Lys Asn Asn Ala L 60 65 70 7.	.eu 15
aac caa ktt gtc cta tgg gac aag att gtt ttg aga ggt gat aat c	cg 393
Asn Gln Xaa Val Leu Trp Asp Lys Ile Val Leu Arg Gly Asp Asn P: 80 85 90	ro
aag ctg ctg aaa gat atg aaa aca aaa tat ttt ttc ttt gac g	
Lys Leu Leu Lys Asp Met Lys Thr Lys Tyr Phe Phe Asp A 95 100 105	rsp
gga aat ggt ctc wag gga aac agg aat gtc act ttg acc ctg tct t	
Gly Asn Gly Leu Xaa Gly Asn Arg Asn Val Thr Leu Thr Leu Ser T 110 115 120	
aac gtc gta cca aat gct gga att cta cct ctt gtg aca gga tca g	
Asn Val Val Pro Asn Ala Gly Ile Leu Pro Leu Val Thr Gly Ser G 125 130 135	Sly
cac gta tot gto coa ttt coa gat aca tat gaa ata acg aag agt to	at 585
His Val Ser Val Pro Phe Pro Asp Thr Tyr Glu Ile Thr Lys Ser T	
140 145 150 1: taaattatto tgaatttgaa acaaaaaaaa aaaahm	.55 621
	621

<210> 378

<211> 52

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -20..-1

<400> 378



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        Met
        Pro
        Ser
        Val
        Asn
        Ser
        Ala
        Gly
        Leu
        Cys
        Val
        Leu
        Gln
        Leu
        Thr
        -5

        Ala
        Val
        Thr
        Ser
        Ala
        Phe
        Leu
        Leu
        Ala
        Lys
        Val
        Asn
        Pro
        Phe
        Glu
        Xaa

        Phe
        Leu
        Ser
        Arg
        Gly
        Phe
        Trp
        Leu
        Cys
        Ala
        Ala
        His
        Phe
        Ile
        His

        Pro
        Cys
        Leu
        Asp
        30
        Ala
        Ala
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<210> 379
<211> 193
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 379
Met Val Val Leu Arg Ala Gly Lys Lys Thr Phe Leu Pro Pro Leu Xaa
                                -15
Arg Ala Phe Ala Cys Arg Gly Cys Gln Leu Ala Pro Glu Arg Gly Ala
Glu Arg Arg Asp Thr Ala Pro Ser Gly Val Ser Arg Phe Cys Pro Pro
                   15
Arg Lys Ser Cys His Asp Trp Ile Gly Pro Pro Asp Lys Tyr Ser Asn
Leu Arg Pro Val His Phe Tyr Ile Pro Glu Asn Glu Ser Pro Leu Glu
                               50
Gln Lys Leu Arg Lys Leu Arg Gln Glu Thr Gln Glu Trp Asn Gln Gln
                           65
Phe Trp Ala Asn Gln Asn Leu Thr Phe Ser Lys Glu Lys Glu Glu Phe
                       80
Ile His Ser Arg Leu Lys Thr Lys Gly Leu Gly Leu Arg Thr Glu Ser
                                        100
Gly Gln Lys Ala Thr Leu Asn Ala Glu Glu Met Ala Asp Phe Tyr Lys
               110
                                    115
Glu Phe Leu Ser Lys Asn Phe Gln Lys His Met Tyr Tyr Asn Arg Asp
           125
                                130
Trp Tyr Lys Arg Asn Phe Ala Ile Thr Phe Phe Met Gly Lys Val Ala
                           145
Leu Glu Arg Ile Trp Asn Lys Leu Lys Gln Lys Gln Lys Lys Arg Ser
                       160
Asn
170
```



Asn Ala Ile Ala Val Leu His Glu Glu Arg Phe Leu Lys Asn Ile Gly 5 10 15

Trp Gly Thr Asp Gln Gly Ile Gly Gly Phe Gly Glu Glu Pro Gly Ile 20 25 30

Lys Ser Xaa Xaa Met Xaa Leu Ile Arg Ser Val Arg Thr Val Met Arg 35 40 45 50

Val Pro Leu Ile Ile Val Asn Ser Ile Ala Ile Val Leu Leu Leu Leu F55 60 65

<210> 381 <211> 198 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1 <400> 381 Met Pro Val Pro Ala Leu Cys Leu Leu Trp Ala Leu Ala Met Val Thr -15 Arg Pro Ala Ser Ala Ala Pro Met Gly Gly Pro Glu Leu Ala Gln His Glu Glu Leu Thr Leu Leu Phe His Gly Thr Leu Gln Leu Gly Gln Ala 15 20 Leu Asn Gly Val Tyr Arg Thr Thr Glu Gly Arg Leu Thr Lys Ala Arg 35 Asn Ser Leu Gly Leu Tyr Gly Arg Thr Ile Glu Leu Leu Gly Gln Glu 50 Val Ser Arg Gly Arg Asp Ala Ala Gln Glu Leu Arg Ala Ser Leu Leu 65 70 Glu Thr Gln Met Glu Glu Asp Ile Leu Xaa Leu Gln Ala Xaa Ala Thr 85 Ala Glu Val Leu Gly Glu Val Ala Gln Ala Gln Lys Val Leu Arg Asp 100 Ser Val Gln Arg Leu Xaa Xaa Gln Leu Xaa Xaa Ala Trp Leu Gly Pro 115 120 Ala Tyr Arg Lys Phe Glu Val Leu Lys Ala Pro Pro Xaa Lys Gln Asn 130 135 His Ile Leu Trp Ala Leu Thr Gly His Val Xaa Arg Gln Xaa Arg Glu 145 150 Met Val Ala Gln Gln Xaa Xaa Leu Xaa Gln Ile Gln Glu Lys Leu His 160 165 Thr Ala Ala Leu Pro Ala

<210> 382 <211> 160 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -55..-1

175

<400> 382
Met Asp Lys Leu Lys Lys Val Leu Ser Gly Gln Asp Thr Glu Asp Arg

<210> 383

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-55
                    -50
                                        -45
Ser Gly Leu Ser Glu Val Val Glu Ala Ser Ser Leu Ser Trp Ser Thr
               -35
                                   -30
                                                        -25
Arg Ile Lys Gly Phe Ile Ala Cys Phe Ala Ile Gly Ile Leu Cys Ser
            -20
                               -15
Leu Leu Gly Thr Val Leu Leu Trp Val Pro Arg Lys Gly Leu His Leu
Phe Ala Val Phe Tyr Thr Phe Gly Asn Ile Ala Ser Ile Gly Ser Thr
                                        20
Ile Phe Leu Met Gly Pro Val Lys Gln Leu Lys Arg Met Phe Glu Pro
               30
                                    35
Thr_Arg_Leu_Ile_Ala_Thr_Ile_Met_Val_Leu_Leu_Cys_Phe_Ala_Leu_Thr
                                50
Leu Cys Ser Ala Phe Trp Trp His Asn Lys Gly Leu Ala Leu Ile Phe
                            65
Cys Ile Leu Gln Ser Leu Ala Leu Thr Trp Tyr Ser Leu Ser Phe Ile
                       80
Pro Phe Ala Arg Asp Ala Val Lys Xaa Cys Phe Ala Val Cys Leu Ala
                   95
                                        100
```

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<211> 108
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -18..-1
<400> 383
Met Lys Ala Leu Cys Leu Leu Leu Pro Val Leu Gly Leu Leu Val
           -15
Ser Ser Lys Thr Leu Cys Ser Met Glu Glu Ala Ile Asn Glu Arg Ile
Gln Glu Val Ala Gly Ser Leu Ile Phe Arg Ala Ile Ser Ser Ile Gly
                    20
Arg Gly Ser Glu Ser Val Thr Ser Arg Gly Asp Leu Ala Thr Cys Pro
                                    40
Arg Gly Phe Ala Val Thr Gly Cys Thr Cys Gly Ser Ala Cys Gly Ser
                                55
Trp Asp Val Arg Ala Glu Thr Thr Cys His Cys Gln Cys Ala Gly Met
                            70
```

Asp Trp Thr Gly Ala Arg Cys Cys Arg Val Gln Pro



- 5 Leu Tyr Ile Pro Xaa Arg Xaa Arg Ser Asp Glu Leu Val Phe Glu Ser 15 20 Gln Lys Gly Ser Ala Met Glu Leu Ala Val Ile Thr Val Xaa Gly Val 35

<210> 385 <211> 27 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -15..-1 <400> 385

Met Gly Phe Leu Xaa Leu Met Thr Leu Thr Thr His Val His Ser Ser -10 Ala Lys Pro Asn Glu Gln Pro Trp Leu Leu Asn

<210> 386 <211> 186 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -21..-1

<400> 386 Met Ser Pro Ser Gly Arg Leu Cys Leu Leu Thr Ile Val Gly Leu Ile

Leu Pro Thr Arg Gly Gln Thr Leu Lys Asp Thr Thr Ser Ser Ser Ala Asp Ser Thr Ile Met Asp Ile Gln Val Pro Thr Arg Ala Pro Asp 20 Ala Val Tyr Thr Glu Leu Gln Pro Thr Ser Pro Thr Pro Thr Trp Pro Ala Asp Glu Thr Pro Gln Pro Gln Thr Gln Thr Gln Gln Leu Glu Gly 50 Thr Asp Gly Pro Leu Val Thr Asp Pro Glu Thr His Xaa Ser Xaa Lys 65 70 Ala Ala His Pro Thr Asp Asp Thr Thr Leu Ser Glu Arg Pro Ser 85 80 Pro Ser Thr Xaa Val His Xaa Arg Pro Xaa Xaa Pro Ser Xaa His Leu 100 Val Phe Met Arg Met Thr Pro Ser Ser Met Met Asn Thr Pro Ser Gly 115 Asn Xaa Gly Cys Trp Ser Gln Leu Cys Cys Ser Ser Gln Ala Ser Ser 130 Ser Ser Pro Val Ala Ser Ala Gly Ser Cys Pro Gly Tyr Ala Gly Ile 145 150 Ile Ala Gly Glu Ser Ile Arg Asn Arg Ser

-15

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<210> 387
<211> 179
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 387
Met Glu Thr Gly Ala Leu Arg Arg Pro Gln Leu Leu Pro Leu Leu
  -15
Leu Leu Cys Gly Pro Ser Gln Asp Gln Cys Arg Pro Val Leu Gln Asn
                   -5
Leu Leu Gln Ser Pro Gly Leu Thr Trp Ser Leu Glu Val Pro Thr Gly
Arg Glu Gly Lys Glu Gly Gly Asp Arg Gly Pro Gly Leu Xaa Gly Ala
                           30
Thr Pro Ala Arg Ser Pro Gln Gly Lys Glu Met Gly Arg Gln Arg Thr
Arg Lys Val Lys Gly Pro Ala Trp Xaa His Thr Ala Asn Gln Glu Leu
                                      65
Asn Arg Met Arg Ser Leu Ser Ser Gly Ser Val Pro Val Gly His Leu
                                  80
Glu Gly Gly Thr Val Lys Leu Gln Lys Asp Thr Gly Leu His Ser Cys
                              95
Xaa Asp Gly Met Ala Ser Leu Glu Gly Thr Pro Ala Ser Val Leu Ala
                           110
Asp Ala Cys Pro Gly Phe His Asp Val Xaa Val Gln Xaa Ala Leu Phe
                       125
                                          130
Gly Leu Ser Gly Xaa Xaa Leu Trp Leu Lys Thr His Phe Cys Leu Ser
135
Ile Xaa Leu
```

```
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -55..-1
<400> 388
Met Ala Thr Thr Val Pro Asp Gly Cys Arg Asn Gly Leu Lys Ser Lys
                    -50
                                        -45
Tyr Tyr Arg Leu Cys Asp Lys Ala Glu Ala Trp Gly Ile Val Leu Glu
                -35
                                    -30
Thr Val Ala Thr Ala Gly Val Val Thr Ser Val Ala Phe Met Leu Thr
                                -15
Leu Pro Ile Leu Val Cys Lys Val Gln Asp Ser Asn Arg Arg Lys Met
Leu Pro Thr Gln Phe Leu Phe Leu Leu Gly Val Leu Gly Ile Phe Gly
Leu Thr Phe Ala Phe Ile Ile Gly Leu Asp Gly Ser Thr Gly Pro Thr
                                   35
Arg Phe Phe Leu Phe Gly Ile Leu Phe Ser Ile Cys Phe Ser Cys Leu
                               50
Leu Ala His Ala Val Ser Leu Thr Lys Leu Val Arg Gly Arg Lys Ala
                            65
                                               70
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<210> 388 <211> 150 <212> PRT



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Pro Phe Pro Val Gly Asp Ser Gly Ser Gly Arg Gly Leu Gln Pro Ser
75 80 85

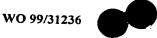
Pro Gly Cys Tyr Arg Tyr
90 95
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<210> 389
<211> 236
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -31..-1
<400> 389
Met Leu Ser Lys Gly Leu Lys Arg Lys Arg Glu Glu Glu Glu Lys
                       -25
                                           -20
Glu Pro Leu Ala Val Asp Ser Trp Trp Leu Asp Pro Gly His Ala Ala
                   -10
                                   - 5
Val Ala Gln Ala Pro Pro Ala Val Ala Ser Ser Leu Phe Asp Leu
                              10
Ser Val Leu Lys Leu His His Ser Leu Gln Xaa Ser Xaa Pro Asp Leu
                           25
Arq His Leu Val Leu Val Xaa Asn Thr Leu Arg Arg Ile Gln Ala Ser
                       40
Met Ala Pro Ala Ala Leu Pro Pro Val Pro Thr Pro Pro Ala Ala
                                       60
Pro Xaa Val Ala Asp Asn Leu Leu Ala Ser Ser Asp Ala Ala Leu Ser
               70
                                   75
Ala Ser Met Ala Xaa Leu Leu Glu Asp Leu Ser His Ile Glu Gly Leu
           85
                               90
Ser Gln Ala Pro Gln Pro Leu Ala Asp Glu Gly Pro Pro Gly Arg Ser
                           105
                                               110
Ile Gly Gly Xaa Pro Pro Xaa Leu Gly Ala Leu Asp Leu Leu Gly Pro
                       120
                                           125
Ala Thr Gly Cys Leu Leu Asp Asn Gly Leu Glu Gly Leu Phe Glu Asp
                                       140
Ile Asp Thr Ser Met Tyr Asp Asn Glu Leu Trp Ala Pro Ala Ser Glu
               150
                                   155
Gly Leu Lys Pro Gly Pro Glu Asp Gly Pro Gly Lys Glu Glu Ala Pro
                               170
           165
Glu Leu Asp Glu Ala Glu Leu Asp Tyr Leu Met Asp Val Leu Val Gly
                          185
Thr Gln Ala Leu Glu Arg Pro Pro Gly Pro Gly Arg
    195
                       200
```

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<210> 390
<211> 149
<212> PRT
<213> Homo sapiens

<220>
<221> SIGNAL
<222> -100..-1

<400> 390
Met Glu Thr Leu Tyr Arg Val Pro Phe Leu Val Leu Glu Cys Pro Asn
-100 -95 -90 -85
```



```
Leu Lys Leu Lys Lys Pro Pro Trp Leu His Met Pro Ser Ala Met Thr
               -80
                                  -75
Val Tyr Ala Leu Val Val Ser Tyr Phe Leu Ile Thr Gly Gly Ile
           -65
                              -60
                                                 -55
Ile Tyr Asp Val Ile Val Glu Pro Pro Ser Val Gly Ser Met Thr Asp
       -50
                          -45
                                              -40
Glu His Gly His Gln Arg Pro Val Ala Phe Leu Ala Tyr Arg Val Asn
                       -30
Gly Gln Tyr Ile Met Glu Gly Leu Ala Ser Ser Phe Leu Phe Thr Met
                   -15
Gly Gly Leu Gly Phe Ile Ile Leu Asp Gly Ser Asn Ala Pro Asn Ile
               1 5
Pro Lys Leu Asn Arg Phe Leu Leu Phe Ile Gly Phe Val Cys Val
                          20
Leu Xaa Ser Phe Xaa Xaa Ala Arg Val Phe Met Arg Met Lys Leu Pro
Gly Tyr Leu Met Gly
```

<210> 391 <211> 69 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -49..-1

45

<400> 391 Met Pro Phe His Phe Pro Phe Leu Gly Phe Val Cys Leu His Leu His -45 -40 Leu Thr Pro Cys Leu Thr Val Pro Arg Pro Leu Phe Leu Leu -30 -25 His Leu Cys Pro His Leu Pro Phe Leu Leu Leu Ser Cys Val Gly -15 -10 -5 Xaa Xaa Pro Ser Cys Leu Pro Ser Ser Ser Thr Cys Val Ser Leu His 10 Phe Phe Ile Pro Asp

<210> 392 <211> 241 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -30..-1

20

<400> 392 Met Gly Thr Ala Ser Arg Ser Asn Ile Ala Arg His Leu Gln Thr Asn -25 -20 Leu Ile Leu Phe Cys Val Gly Ala Val Gly Ala Cys Thr Leu Ser Val -10 - 5 Thr Gln Pro Trp Tyr Leu Glu Val Asp Tyr Thr His Glu Ala Val Thr 10 Ile Lys Cys Thr Phe Ser Ala Thr Gly Cys Pro Ser Glu Gln Pro Thr 20 25



Cys Leu Trp Phe Arg Tyr Gly Ala His Gln Pro Glu Asn Leu Cys Leu 40 45 Asp Gly Cys Lys Ser Glu Ala Xaa Lys Phe Thr Val Arg Glu Ala Leu 55 60 Lys Glu Asn Gln Val Ser Leu Thr Val Asn Arg Val Thr Ser Asn Asp 70 75 Ser Ala Ile Tyr Ile Cys Gly Ile Ala Phe Pro Ser Val Pro Glu Ala 90 95 Arg Ala Lys Gln Thr Gly Gly Gly Thr Thr Leu Val Val Arg Glu Ile 105 110 Lys Leu Leu Ser Lys Glu Leu Arg Ser Phe Leu Thr Ala Leu Val Ser 115 120 125 Leu Leu Ser Val Tyr Val Thr Gly Val Cys Val Ala Phe Ile Leu Leu 135 140 Ser Lys Ser Lys Ser Asn Pro Leu Arg Asn Lys Glu Ile Lys Glu Asp 150 155 Ser Gln Lys Lys Lys Ser Ala Arg Arg Ile Phe Gln Glu Ile Ala Gln 170 175 Glu Leu Tyr His Lys Arg His Val Glu Thr Asn Gln Gln Ser Glu Lys 185 190 Asp Asn Asn Thr Tyr Glu Asn Arg Arg Val Leu Ser Asn Tyr Glu Arg 200 205 Pro

<210> 393 <211> 47 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -30..-1

<210> 394 <211> 65 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -28..-1

30

35

Ser

<210> 395 <211> 73 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -24..-1

<400> 395

Met Thr Cys Trp Met Leu Pro Pro Ile Ser Phe Leu Ser Tyr Leu Pro -20 -15 Leu Trp Leu Gly Pro Ile Trp Pro Cys Ser Gly Ser Thr Leu Gly Lys Pro Asp Pro Gly Val Trp Pro Ser Leu Phe Arg Pro Trp Asp Ala Ala 15 20 Ser Pro Gly Asn Tyr Ala Leu Ser Arg Gly Xaa Asn Xaa Tyr Xaa Xaa 30 Trp Gly Gln Gly Thr His Ser Ser Leu 45

<210> 396 <211> 60 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -18..-1 <400> 396 Met Pro Cys Pro Thr Trp Thr Cys Leu Lys Ser Phe Pro Ser Pro Thr -15 Ser Ser His Ala Ser Ser Leu His Leu Pro Pro Ser Cys Thr Arg Leu 5

10 Thr Leu Thr Gln Thr Leu Arg Thr Gly Met His Leu Ser Arg Ala Leu 20 Gln Gly Thr Leu Thr Arg Leu Gln Ser Thr Pro Ala 35

-10

<210> 397 <211> 192 <212> PRT <213>-Homo-sapiens

<220> <221> SIGNAL <222> -93..-1

<400> 397 Met Ala Glu Leu Gly Leu Asn Glu His His Gln Asn Glu Val Ile Asn -90 -85 Tyr Met Arg Phe Ala Arg Ser Lys Arg Gly Leu Arg Leu Lys Thr Val



-70 -65 Asp Ser Cys Phe Gln Asp Leu Lys Glu Ser Arg Leu Val Glu Asp Thr -55 -50 Phe Thr Ile Asp Glu Val Ser Glu Val Leu Asn Gly Leu Gln Ala Val -40 -35 Val His Ser Glu Val Glu Ser Glu Leu Ile Asn Thr Ala Tyr Thr Asn -25 -20 Val Leu Leu Arg Gln Leu Phe Ala Gln Ala Glu Lys Trp Tyr Leu -5 Lys Leu Gln Thr Asp Ile Ser Glu Leu Glu Asn Arg Glu Leu Leu Glu 10 Gln Xaa Ala Glu Phe Glu Lys Ala Xaa Ile Thr Ser Ser Asn Lys Lys 25 Pro Ile Leu Xaa Val Thr Xaa Pro Lys Leu Ala Pro Leu Asn Glu Gly 45 Gly Thr Ala Lys Leu Leu Asn Lys Val Ile Cys Ile Ile Leu Arg Asn 60 Gly Lys Ser Leu Ile Leu Ser Cys His Cys Leu Gly Trp Arg Asn Lys 75 Ser Gly Arg Phe Val Ser Gly Pro Leu Arg Ile Ile Ser Pro Leu Gln

<210> 398

<211> 149

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -72..-1

<400> 398

Met Asn Leu Phe Ile Met Tyr Met Ala Gly Asn Thr Ile Ser Ile Phe -65

Pro Thr Met Met Val Cys Met Met Ala Trp Arg Pro Ile Gln Ala Leu -50 -45

Met Ala Ile Ser Ala Thr Phe Lys Met Leu Glu Ser Ser Ser Gln Lys -35 -30

Phe Leu Gln Gly Leu Val Tyr Leu Ile Gly Asn Leu Met Gly Leu Ala

-15 Leu Ala Val Tyr Lys Cys Gln Ser Met Gly Leu Leu Pro Thr His Ala

Ser Asp Trp Leu Ala Phe Ile Glu Pro Pro Glu Arg Met Glu Ser Val 15 20

Val Glu Asp Cys Phe Cys Glu His Glu Lys Ala Ala Pro Gly Pro Tyr 30

Val Phe Gly Ser Tyr Leu His Pro Ser Leu Ser Pro Val Ala Pro Gln 45 50

His Thr Leu Lys Leu Ile Thr Tyr Val Lys Lys Asn Gln Lys Thr Leu 60

Phe Ser Met Val Gly

75

<210> 399

<211> 73

<212> PRT

<213> Homo sapiens

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<211> 86
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -20..-1
<400> 400
Met Asn Leu His Phe Pro Gln Trp Phe Val His Ser Ser Ala Leu Gly
                  -15
                                       -10
Leu Val Leu Ala Pro Pro Phe Ser Ser Pro Gly Thr Asp Pro Thr Phe
Pro Cys Ile Tyr Cys Arg Leu Leu Asn Met Ile Met Thr Arg Leu Ala
                            20
Phe Ser Phe Ile Thr Cys Leu Cys Pro Asn Leu Lys Glu Val Cys Leu
                       35
Ile Leu Pro Glu Lys Asn Cys Asn Ser Arg His Ala Gly Phe Val Gly
```

45 50 55 60
Pro Xaa Lys Leu Arg Gln
65

```
<210> 401
<211> 78
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
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<210> 400

PCT/IB98/02122

45

50

55

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<210> 402
<211> 65
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -28..-1
<400> 402
Met Gly Lys Gly His Gln Arg Pro Trp Trp Lys Val Leu Pro Leu Ser
                         -20
           -25
Cys Phe Leu Val Ala Leu Ile Ile Trp Cys Tyr Leu Arg Glu Glu Ser
       -10
                            -5
Glu Ala Asp Gln Trp Leu Arg Gln Val Trp Gly Glu Val Pro Glu Pro
                   10
Ser Asp Arg Ser Glu Glu Pro Glu Thr Pro Ala Ala Tyr Arg Ala Arg
               25
Thr
<210> 403
<211> 211
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -27..-1
<400> 403
Met Leu Leu Ser Ile Thr Thr Ala Tyr Thr Gly Leu Glu Leu Thr
                            -20
Phe Phe Ser Gly Val Tyr Gly Thr Cys Ile Gly Ala Thr Asn Lys Phe
                       -5
Gly Ala Glu Glu Xaa Ser Leu Ile Gly Leu Ser Gly Ile Phe Ile Gly
                                    15
Ile Gly Glu Ile Leu Gly Gly Ser Leu Phe Gly Leu Leu Ser Lys Asn
                                30
Asn Arg Phe Gly Arg Asn Pro Val Val Leu Leu Gly Ile Leu Val His
                            45
Phe Ile Ala Phe Tyr Leu Ile Phe Leu Asn Met Pro Gly Asp Ala Pro
                        60
Ile Ala Pro Val Lys Gly Thr Asp Ser Ser Ala Tyr Ile Lys Ser Ser
                    75
                                        80
Lys Xaa Phe Ala Ile Leu Cys Xaa Phe Leu Xaa Gly Leu Gly Asn Ser
                90
Cys Phe Asn Thr Xaa Leu Leu Xaa Ile Xaa Gly Phe Leu Tyr Ser Glu
                                110
                                                    115
Xaa Ser Ala Pro Xaa Phe Ala Ile Phe Asn Phe Val Gln Ser Ile Cys
                            125
                                                130
```

Ala Ala Val Ala Phe Phe Tyr Ser Asn Tyr Leu Leu Leu His Trp Gln

Leu Leu Val Met Val Ile Phe Gly Phe Xaa Gly Thr Ile Ser Phe Phe

Thr Val Glu Trp Glu Xaa Ala Ala Phe Val Xaa Arg Gly Ser Asp Tyr

145

160

175

140

155

Arg Ser Ile

<210> 405

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<210> 404
<211> 123
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -80..-1
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<400> 404 Met Ser Thr Trp Tyr Leu Ala Leu Asn Lys Ser Tyr Lys Asn Lys Asp -75 -70 Ser Val Arg lle Tyr Leu Ser Leu Cys Thr Val Ser Ile Lys Phe Thr -60 -55 Tyr Phe His Asp Ile Gln Thr Asn Cys Leu Thr Thr Trp Lys His Ser -40 Arg Cys Arg Phe Tyr Trp Ala Phe Gly Gly Ser Ile Leu Gln His Ser -25 -20 Val Asp Pro Leu Val Leu Phe Leu Ser Leu Ala Leu Leu Val Thr Pro -10 Thr Ser Thr Pro Ser Ala Lys Ile Gln Ser Leu Gln Ile Asp Leu Pro 10 Gly Gly Trp Arg Leu Ala Thr Asp Arg Ile Phe Thr Leu Ser Pro Val 25 Pro Met Asp Xaa Pro Leu Ile Leu His Gln Leu

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<211> 86
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 405
Met Glu Lys Ser Trp Met Leu Trp Asn Phe Val Glu Arg Trp Leu Ile
                      -20
                                        -15
Ala Leu Ala Ser Trp Ser Trp Ala Leu Cys Arg Ile Ser Leu Leu Pro
                  -5
Leu Ile Val Thr Phe His Leu Tyr Gly Gly Ile Ile Leu Leu Leu
           10
                             15
Ile Phe Ile Ser Ile Xaa Gly Ile Leu Tyr Lys Phe Xaa Asp Val Leu
                         30
Leu Tyr Phe Pro Xaa Gln Xaa Ser Ser Ser Arg Leu Tyr Asp Ser His
45
Ala His Trp Xaa Ser Xaa
```

```
<210> 406
<211> 162
<212> PRT
<213> Homo sapiens
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```
<220>
<221> SIGNAL
<222> -31..-1
```

<400> 406

Met Ala Ala Ala Trp Pro Ser Gly Pro Xaa Ala Pro Glu Ala Val Thr
-30 -25 -20

Ala Arg Leu Val Gly Val Leu Trp Phe Val Ser Val Thr Thr Gly Pro
-15 -5 1

Trp Gly Ala Val Ala Thr Ser Ala Gly Gly Glu Glu Ser Leu Lys Cys
5 10 15

Glu Asp Leu Lys Val Gly Gln Tyr Ile Cys Lys Asp Pro Lys Ile Asn 20 25 30

Asp Ala Thr Gln Glu Pro Val Asn Cys Thr Asn Tyr Thr Ala His Val

Ser Cys Phe Pro Ala Pro Asn Ile Thr Cys Lys Asp Ser Ser Gly Asn 50 55 60 65

Glu Thr His Phe Thr Gly Asn Glu Val Gly Phe Phe Lys Pro Ile Ser

Cys Arg Asn Val Asn Gly Tyr Ser Tyr Asn Glu Gln Ser His Val Ser 85 90 95

Phe Ser Trp Met Val Gly Ser Arg Ser Ile Leu Pro Trp Ile Pro Cys 100 105 110

Phe Gly Phe Val Lys Xaa Xaa His Cys Arg Val Xaa Trp Asn Trp Glu 115 120 125

Pro Asn

130

<210> 407

<211> 98

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -37..-1

<400> 407

Met Ala Ser Leu Leu Cys Cys Gly Pro Lys Leu Ala Ala Cys Gly Ile
-35 -30 -25

Val Leu Ser Ala Trp Gly Val Ile Met Leu Ile Met Leu Gly Ile Phe
-20 -15 -10

Phe Asn Val His Ser Ala Val Leu Ile Glu Asp Val Pro Phe Thr Glu
-5 1 5 10

Lys Asp Phe Glu Asn Gly Pro Gln Asn Ile Tyr Asn Leu Tyr Xaa Gln
15 20 25

Xaa Ser Tyr Asn Cys Phe Ile Ala Ala Gly Leu Tyr Leu Leu Gly
30 35 40

Gly Phe Ser Phe Cys Gln Xaa Arg Leu Asn Lys Arg Lys Glu Tyr Met

Val Arg

60

<210> 408

<211> 70

<212> PRT

<213> Homo sapiens



```
<220>
 <221> SIGNAL
 <222> -15..-1
 <400> 408
 Met Arg Phe Leu Pro Cys Cys Leu Leu Trp Ser Val Phe Asn Pro Glu
 -15
                     -10
                                 -5
 Ser Leu Asn Cys His Tyr Phe Xaa Xaa Glu Xaa Cys Ile Phe Xaa Ser
 Leu Gln Tyr Tyr Glu Ile Ser Leu Gln Glu Lys Leu Leu Gly Phe Leu
                             25
 Trp Leu Cys Phe Leu Ser Tyr Phe Phe Arg Ala Val Tyr Phe Leu Ile
                         40
 Asp Phe Ser Ser Phe Thr
 50
<210> 409
<211> 60
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -45..-1
<400> 409
Met His Ser Leu Phe Ile Ala Ser Leu Lys Val Leu Phe Tyr Tyr Ser
-45
                    -40
                                        -35
Phe Ser Phe Arg Phe Asn Trp Phe Asp Cys Leu Leu His Asn Leu Gly
                -25
                                    -20
Glu Asn Phe Leu Ser Leu Leu Ser Lys Ser Cys Ser Ala Asp Pro Ser
           -10
                                - 5
Gly Ser Thr Phe Met Arg Asp Ile Glu Thr Asn Lys
    5
                        10
<210> 410
<211> 39
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -22..-1
<400> 410
Met Pro Glu Ala Val Glu Gln Ser Ala His Leu Phe Val Thr Trp Ser
```

-15

1

Ser Gln Arg Ala Leu Ser His Pro Ala Pro Phe Leu Thr Xaa Xaa Lys

-10

5

<210> 411 <211> 51

Asn Pro Phe Leu Trp Lys Leu

15

<212> PRT



```
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 411
Met Ala Phe Gln Ser Leu Leu Glu Met Lys Phe Phe Leu Cys Ala Ala
           -20
                               -15
                                                    -10
Phe Pro Leu Gly Ala Gly Val Lys Met Phe His Tyr Leu Gly Pro Gly
                           1
Lys Pro Leu Xaa Gln Ala Ser Pro Ser Pro His Pro His Arg Xaa Arg
                  15
Ile Trp Pro
<210> 412
<211> 95
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -48..-1
<400> 412
Met Ala Ser Ser His Trp Asn Glu Thr Thr Thr Ser Val Tyr Gln Tyr
            -45
                                -40
Leu Gly Phe Gln Val Gln Lys Ile Tyr Pro Phe His Asp Asn Trp Asn
       -30
                           -25
                                               -20
Thr Ala Cys Phe Val Ile Leu Leu Phe Ile Phe Thr Val Val Ser
   -15
                       -10
                                           - 5
Leu Val Val Leu Ala Phe Leu Tyr Glu Val Leu Xaa Xaa Cys Cys Cys
                                   10
Val Lys Asn Lys Thr Val Lys Asp Leu Lys Ser Glu Pro Asn Pro Leu
          20
                               25
Xaa Xaa Met Met Asp Asn Ile Arg Lys Arg Glu Thr Glu Val Val
<210> 413
<211> 60
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -32..-1
<400> 413
Met Asp Glu Tyr Ser Trp Trp Cys His Val Leu Glu Val Val Lys Gly
                            -25
Gln Met Phe Thr Phe Ile Asn Ile Thr Leu Trp Leu Gly Ser Leu Cys
                        -10
                                            - 5
Gln Arg Phe Phe Tyr Ala Ser Gly Thr Tyr Phe Leu Ile Tyr Ile Ser
                                   10
```

Thr Val Thr Pro Ser Trp Arg Leu Cys Leu Val Ser

25



```
<210> 414
<211> 170
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -79..-1
```

## <400> 414

<210> 415 <211> 190

Met Glu Asp Pro Asn Pro Glu Glu Asn Met Lys Gln Gln Asp Ser Pro -70 Lys Glu Arg Ser Pro Gln Ser Pro Gly Gly Asn Ile Cys His Leu Gly -55 Ala Pro Lys Cys Thr Arg Cys Leu Ile Thr Phe Ala Asp Ser Lys Phe -40 Gln Glu Arg His Met Lys Arg Glu His Pro Ala Asp Phe Val Ala Gln -25 -20 Lys Leu Gln Gly Val Leu Phe Ile Cys Phe Thr Cys Ala Arg Ser Phe -10 -5 Pro Ser Ser Lys Ala Xaa Xaa Thr His Gln Arg Ser His Gly Pro Xaa 10 Ala Lys Pro Thr Leu Pro Val Ala Thr Thr Thr Ala Gln Pro Thr Phe 25 Pro Cys Pro Asp Cys Gly Lys Thr Phe Gly Gln Ala Val Ser Leu Xaa 40 Arg His Xaa Gln Xaa His Glu Val Arg Ala Pro Pro Gly Thr Phe Ala 55 60 Cys Thr Xaa Cys Gly Gln Asp Phe Ala Gln Glu Xaa Gly Leu His Gln 70 His Tyr Ile Arg His Ala Arg Gly Gly Leu

```
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -82..-1
<400> 415
Met Tyr Val Trp Pro Cys Ala Val Val Leu Ala Gln Tyr Leu Trp Phe
                            -75
His Arg Arg Ser Leu Pro Gly Lys Ala Ile Leu Glu Ile Gly Ala Gly
                        -60
Val Ser Leu Pro Gly Ile Leu Ala Ala Lys Cys Gly Ala Glu Val Ile
                                        -40
Leu Ser Asp Ser Ser Glu Leu Pro His Cys Leu Glu Val Cys Arg Gln
                                    -25
Ser Cys Gln Met Asn Asn Leu Pro His Leu Gln Val Val Gly Leu Thr
                                -10
Trp Gly His Ile Ser Trp Asp Leu Leu Ala Leu Pro Pro Gln Asp Ile
                       5
Ile Leu Ala Ser Asp Val Phe Phe Glu Pro Glu Xaa Phe Glu Asp Ile
                20
                                       25
Leu Ala Thr Ile Tyr Phe Leu Met His Lys Asn Pro Lys Val Gln Leu
               35
```



Trp Ser Thr Tyr Gln Val Arg Xaa Ala Asp Trp Ser Leu Glu Ala Leu 50 55 60

Leu Tyr Lys Trp Asp Met Lys Cys Val His Ile Pro Leu Glu Ser Phe 65 70 75

Asp Ala Asp Lys Glu Xaa Ile Ala Glu Ser Thr Leu Pro Gly Arg His 80 85 90

Thr Val Glu Met Leu Val Ile Ser Phe Ala Lys Asp Ser Leu 95

<210> 416 <211> 114 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -60..-1 <400> 416 Met Met Ala Ala Val Pro Pro Gly Leu Glu Pro Trp Asn Arg Val Arg -55 -50 Ile Pro Lys Ala Gly Asn Arg Ser Ala Val Thr Val Gln Asn Pro Gly -40 -35 Ala Ala Leu Asp Leu Cys Ile Ala Ala Val Ile Lys Glu Cys His Leu -25 -20 Val Ile Leu Ser Leu Lys Ser Gln Thr Leu Asp Ala Glu Thr Asp Val -5 Leu Cys Ala Val Leu Tyr Ser Asn His Asn Arg Met Gly Arg His Lys 10 15 Pro His Leu Ala Leu Lys Gln Val Glu Gln Cys Leu Lys Arg Leu Lys 30 Asn Met Asn Leu Glu Gly Ser Ile Gln Asp Leu Phe Glu Leu Phe Ser

<210> 417 <211> 161 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<400> 417

<222> -108..-1

Ser Lys

 Met
 Thr
 Ser
 Gly
 Gln
 Ala
 Arg
 Ala
 Ser
 Xaa
 Gln
 Ser
 Pro
 Gln
 Ala
 Leu

 -105
 -100
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<210> 418



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-10
His Arg Thr Val Phe Leu Thr Arg Thr Ala Thr Pro Arg Ser Gly Thr 5
Arg Ser Ser Gln Leu Pro Glu Met Pro Thr Gln Asn Thr Pro Lys Ile 25
Thr Ile Leu Ser Gly Val Ile Arg Gly Pro Leu Glu Lys Ser Ile Met 40
Leu
```

```
<211> 67
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 418
Met Leu Gly Gly Asp His Arg Ala Leu Leu Leu Lys Ile Trp Leu Leu
                        -15
Gln Arg Pro Glu Ser Gln Glu Gly Leu Leu Pro Gly Arg Leu Val Val
Met Glu Arg Arg Val Lys Asn Asp Leu Met Ser Phe Leu Ser Thr Val
                               20
Leu Leu Ser Phe His Ser Ser Asn Ala Arg Val Ser His Cys Glu Pro
    30
                            35
Leu Arg Met
  45
```

<210> 419
<211> 332
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -32..-1

100

<400> 419 Met Ile Xaa Leu Arg Asp Thr Ala Ala Ser Leu Arg Leu Glu Arg Asp -25 -20 Thr Arg Gln Leu Pro Leu Leu Thr Ser Ala Leu His Gly Leu Gln Gln -10 -5 Gln His Pro Ala Phe Ser Gly Val Ala Arg Leu Ala Lys Arg Trp Val Arg Ala Gln Leu Leu Gly Glu Gly Phe Ala Asp Glu Ser Leu Asp Leu 20 25 Val Ala Ala Ala Leu Phe Leu His Pro Glu Pro Phe Thr Pro Pro Ser Ser Pro Gln Val Gly Phe Leu Arg Phe Leu Phe Leu Val Ser Thr Phe Asp Trp Lys Asn Asn Pro Leu Phe Val Asn Leu Asn Asn Glu Leu Thr 70 Val Glu Glu Gln Val Glu Ile Arg Ser Gly Phe Leu Ala Ala Arg Ala 90 Gln Leu Pro Val Met Val Ile Val Thr Pro Gln Xaa Arg Lys Asn Ser



```
Val Trp Thr Gln Asp Gly Pro Ser Ala Gln Ile Leu Gln Gln Leu Val
        115
                           120
                                               125
Val Leu Ala Ala Glu Xaa Leu Pro Met Leu Xaa Xaa Gln Leu Met Asp
                       135
                                           140
Pro Arg Gly Pro Gly Asp Ile Arg Thr Xaa Phe Arg Pro Pro Leu Asp
                    150
                                       155
Ile Tyr Asp Val Leu Ile Arg Leu Ser Pro Arg His Ile Pro Arg His
               165
                                   170
                                                     175
Arg Gln Ala Val Asp Ser Pro Ala Ala Ser Phe Cys Arg Gly Leu Leu
           180
                               185
                                                   190
Ser Gln Pro Gly Pro Ser Ser Leu Met Pro Val Leu Gly Xaa Asp Pro
       195
                           200
                                               205
Pro Gln Leu Tyr Leu Thr Gln Leu Xaa Glu Ala Phe Gly Asp Leu Ala
   210
                       215
                                           220
Leu Phe Phe Tyr Asp Gln His Gly Glu Val Ile Gly Val Leu Trp
                   230
                                       235
Lys Pro Thr Ser Phe Gln Pro Gln Pro Phe Lys Ala Ser Ser Thr Lys
               245
                                   250
Gly Arg Met Val Met Ser Arg Gly Glu Leu Val Met Val Pro Asn
           260
                               265
Val Glu Ala Ile Leu Glu Asp Phe Ala Val Leu Gly Glu Gly Leu Val
                           280
Gln Thr Val Glu Ala Arg Ser Glu Arg Trp Thr Val
                       295
```

<210> 420 <211> 65 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -19..-1 <400> 420 Met Gly Gly Ile Trp Asn Ala Leu Ser Met Ser Ser Phe Ser Phe His -10 -15 Ser Ser Ser Cys Ser Ala Leu Ser Ala Lys Ser Leu Leu Ser Arg His 10 His Ile Leu Gln Gln Phe Leu Val Arg Lys Ser Val Pro Leu Glu Asn 20 25 Ala Ser Leu Pro Phe Pro His Leu Gly Ser Ser Leu Phe Lys Ile Val 30 35 Gly



```
-10 -5 1

Arg Val Tyr His Tyr Phe Gln Trp Arg Arg Ala Gln Arg Gln Ala Ala
5 10 15

Glu Glu Gln Lys Xaa Ser Gly Ile Met
20 25
```

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<210> 422
<211> 85
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -17..-1
```

<210> 423
<211> 85
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -17..-1

Leu Pro Ser Glu Lys

65

<400> 423

<210> 424 <211> 69 <212> PRT <213> Homo sapiens



```
<220>
<221> SIGNAL
<222> -29..-1
<400> 424
Met Thr Cys Arg Gly Ser Cys Ser Tyr Ala Thr Arg Arg Ser Pro Ser
            -25
                                -20 -15
Glu Leu Ser Leu Leu Pro Ser Ser Leu Trp Val Leu Ala Thr Ser Ser
           -10
                                -5
Pro Thr Ile Thr Ile Ala Leu Ala Met Ala Ala Gly Asn Leu Cys Pro
                       10
Leu Pro Ser Ser Xaa Arg Xaa Lys Arg Arg Trp Cys Gln Ala Xaa Gln
                   25
                                       30
Gln Xaa Ala Leu Leu
               40
<210> 425
<211> 122
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -56..-1
<400> 425
Met Val Pro Trp Pro Arg Gly Lys Val Lys Thr Ala Pro Ile Pro Ile
                       -50
Ser Arg Phe Pro Phe Leu Pro Thr His Asp Pro Pro Thr Pro Ala His
                   -35
                                       -30
Trp Ser Pro Ala Ser His Gln Gln Phe Lys His Xaa Ser Pro Leu Leu
               -20
                                   -15
Thr Leu Ala Leu Leu Gly Gln Cys Ser Leu Phe Xaa Asn Leu Arg Lys
           -5
Lys Leu Ala Gly Gln Lys Ala Lys Lys Leu Pro Ser Phe Ser Ser Leu
                       15
Pro Leu Thr Leu Trp Pro Leu Thr Pro Gln Phe Ala Glu Leu Thr Thr
25
                   30
                                       35
Val Ala Gln Lys Lys Leu Arg Trp Ser Gly Thr Leu Gly Trp Gly Pro
                                   50
               45
Val Pro Ser Trp Val Gln Phe Phe Leu Gly
            60
<210> 426
<211> 41
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -30..-1
```

Met Ala Cys Glu Thr His Gly Val Leu Val Pro Ala His Leu Ser Gly

Leu Ile Thr Cys Leu Leu Ala Phe Trp Val Pro Ala Ser Cys Ile Gln

-20

- 5

-25

-10

<400> 426

Arg Cys Ser Gly Ser Pro Leu Pro Leu
5 10

<210> 427
<211> 50
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -36..-1

<210> 428
<211> 136
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -18..-1

<400> 428

-15 -10 Xaa Ala Gly Val Gly Tyr Ala Leu Leu Val Ile Val Thr Pro Gly Glu 10 Arg Arg Lys Gln Glu Met Leu Lys Glu Met Pro Leu Gln Asp Pro Arg 20 25 30 Ser Arg Glu Glu Ala Ala Arg Thr Gln Gln Leu Leu Ala Thr Leu 40 Gln Glu Ala Ala Thr Thr Gln Glu Asn Val Ala Trp Arg Lys Asn Trp 55 Met Val Gly Gly Gly Gly Ala Thr Gly Xaa His Arg Glu Thr Gly 70 Leu Ala Ser Val Gly Ala Gly Pro Trp Leu Gly Arg Arg Asn Pro Arg 90 Gln Leu Ser Pro Ser Trp Ala Xaa Arg Lys Ile Arg Xaa Glu Asn Xaa 100 Met Pro Gly Leu Ser Gly Val Leu 115

Met Asp Ser Leu Arg Lys Met Leu Ile Ser Val Ala Met Leu Gly Ala

<210> 429 <211> 194 <212> PRT <213> Homo sapiens

<220>



<221> SIGNAL <222> -65..-1

<400> 429

Met Gln Asp Ala Pro Leu Ser Cys Leu Ser Pro Thr Lys Trp Ser Ser -60 -55 Val Ser Ser Ala Asp Ser Thr Glu Lys Ser Ala Ser Ala Ala Gly Thr -45 -40 Arg Asn Leu Pro Phe Gln Phe Cys Leu Arg Gln Ala Leu Arg Met Lys -30 -25 Ala Ala Gly Ile Leu Thr Leu Ile Gly Cys Leu Val Thr Gly Val Glu -10 Ser Lys Ile Tyr Thr Arg Cys Lys Leu Ala Lys Ile Phe Ser Arg Ala 10 Gly Leu Asp Asn Xaa Arg Gly Phe Ser Leu Gly Asn Trp Ile Cys Met 25 Ala Tyr Tyr Glu Ser Gly Tyr Asn Thr Thr Ala Gln Thr Val Leu Asp

Asp Gly Ser Ile Asp Tyr Gly Ile Phe Gln Ile Asn Ser Phe Ala Trp

Cys Arg Arg Gly Lys Leu Lys Glu Asn Asn His Cys His Val Ala Cys 70

Ser Ala Leu Xaa Thr Asp Asp Leu Thr Asp Ala Ile Ile Cys Ala Xaa 85

Lys Ile Val Lys Glu Thr Gln Gly Met Asn Tyr Trp Gln Gly Trp Lys 100 105

Lys His Cys Glu Gly Arg Asp Leu Ser Xaa Trp Lys Lys Gly Cys Glu 120

Val Ser

<210> 430

<211> 141

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -69..-1

<400> 430

Met Thr Ser Gln Pro Val Pro Asn Glu Thr Ile Ile Val Leu Pro Ser

-65 -60 Asn Val Ile Asn Phe Ser Gln Ala Glu Lys Pro Glu Pro Thr Asn Gln

-50 -45 Gly Gln Asp Ser Leu Lys Lys His Leu His Ala Glu Ile Lys Val Ile

-30 -25

Gly Thr Ile Gln Ile Leu Cys Gly Met Met Val Leu Ser Leu Gly Ile -15 -10

Ile Leu Ala Ser Ala Ser Phe Ser Pro Asn Phe Thr Gln Val Thr Ser

Thr Leu Leu Asn Ser Ala Tyr Pro Phe Ile Gly Pro Phe Phe Val Xaa 15 20

Lys Xaa Ser Glu Glu Gly Arg Met Gly Gln Xaa Gly Glu Glu Xaa Xaa 35

Asn Ser Leu Asn Phe Pro Xaa Ala Ser Leu Leu Xaa Leu Ile Cys Gln 50

Xaa Gln Gly Phe Asn Gly Glu Ser Cys Ser Pro Val Gly



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<210> 431
<211> 248
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -69..-1
```

<400> 431

Met Thr Ser Gln Pro Val Pro Asn Glu Thr Ile Ile Val Leu Pro Ser -65 Asn Val Ile Asn Phe Ser Gln Ala Glu Lys Pro Glu Pro Thr Asn Gln -50 -45 Gly Gln Asp Ser Leu Lys Lys His Leu His Ala Glu Xaa Lys Val Ile -35 🦠 -30 Gly Thr Ile Gln Ile Leu Cys Gly Met Met Val Leu Ser Leu Gly Ile -15 -10 Ile Leu Ala Ser Ala Ser Phe Ser Pro Asn Phe Thr Gln Val Thr Ser Thr Leu Leu Asn Ser Ala Tyr Pro Phe Ile Gly Pro Phe Phe Phe Ile 20 Ile Ser Gly Ser Leu Ser Ile Ala Thr Lys Lys Arg Leu Thr Asn Leu 35 Leu Val His Thr Thr Leu Val Gly Ser Ile Leu Ser Ala Leu Ser Ala 50 Leu Val Gly Phe Ile Xaa Leu Ser Val Lys Gln Ala Thr Leu Asn Pro 70 Ala Ser Leu Xaa Cys Glu Leu Xaa Lys Asn Asn Ile Pro Thr Xaa Xaa 85 Tyr Val Xaa Tyr Phe Tyr His Asp Ser Leu Tyr Thr Thr Asp Xaa Tyr 100 Thr Ala Lys Ala Xaa Leu Ala Gly Thr Leu Ser Leu Met Leu Ile Cys 115 Thr Leu Leu Glu Phe Cys Xaa Xaa Val Leu Thr Ala Val Leu Arg Trp 130 135 Lys Gln Ala Tyr Ser Asp Phe Pro Gly Ser Val Leu Phe Leu Pro Xaa 145 150 Ser Tyr Ile Gly Asn Ser Gly Met Ser Ser Lys Met Thr His Asp Cys 160 Gly Tyr Glu Glu Leu Leu Thr Ser 175

Phe

```
<210> 433
<211> 86
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -14..-1
```

70

<210> 434

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<211> 144
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -58..-1
<400> 434
Met Thr Arg Leu Cys Leu Pro Arg Pro Glu Ala Arg Glu Asp Pro Ile
                                -50
                                                    -45
Pro Val Pro Pro Arg Gly Leu Gly Ala Gly Glu Gly Ser Gly Ser Pro
                            -35
Val Arg Pro Pro Val Ser Thr Trp Gly Pro Ser Trp Ala Gln Leu Leu
                        -20
Asp Ser Val Leu Trp Leu Gly Ala Leu Gly Leu Thr Ile Gln Ala Val
Phe Ser Thr Thr Gly Pro Ala Leu Leu Leu Leu Val Ser Phe Leu
           10
Thr Phe Asp Leu Leu His Arg Pro Ala Val Thr Leu Cys His Ser Ala
                            30
                                                35
Asn Phe Ser Pro Gly Ala Arg Val Arg Gly Pro Val Lys Val Leu Asp
                        45
Ser Arg Arg Leu Tyr Ser Cys Lys Trp Val Gln Ser Gln Asp Asn Leu
                                        65
Ala Ser Arg Lys His Cys Cys Cys Cys Ser Trp Gly Trp Ala Arg Ser
```

80

<210> 435 <211> 121 <210> 436



```
<212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -16..-1
 <400> 435
 Met Glu Arg Leu Val Leu Thr Leu Cys Thr Leu Pro Leu Ala Val Ala
                         -10
 Ser Ala Gly Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln
                 5
 Cys Phe Lys Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser
                                 25
 Pro Leu Asp Gln Val Cys Ile Ser Asn Glu Val Val Val Ser Phe Ser
                             40
Glu Ser Pro Pro Gly Arg Gly Xaa Val Pro Xaa Ala Gly Glu Xaa Pro
                         55
Val Pro Pro Pro Leu Xaa Asp Leu Xaa Met Thr Pro Arg Xaa Xaa Arg
                     70
Ala Trp Gly Pro Val Gly Pro Lys Val Pro Pro Ala Val Ser Pro Ala
Leu Gly Ser Gly Glu His Pro Xaa Xaa
            100
```

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<211> 162
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 436
Met Glu Arg Leu Val Leu Thr Leu Cys Thr Leu Pro Leu Ala Val Ala
                       -10
Ser Ala Gly Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln
Cys Phe Lys Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser
           20
Pro Leu Asp Gln Val Cys Ile Ser Asn Glu Val Val Val Ser Phe Lys
                           40
Trp Ser Val Arg Val Leu Leu Ser Lys Arg Cys Ala Pro Arg Cys Pro
                       55
Asn Asp Asn Met Xaa Phe Glu Trp Ser Pro Ala Pro Met Val Gln Gly
                   70
Val Ile Thr Arg Arg Cys Cys Ser Trp Ala Leu Cys Asn Arg Ala Leu
               85
Thr Pro Gln Glu Gly Arg Trp Ala Leu Xaa Gly Gly Leu Leu Gln
100 105 110
Asp Pro Ser Arg Gly Xaa Lys Thr Trp Val Arg Pro Gln Leu Gly Leu
                           120
                                              125
Pro Leu Cys Leu Pro Xaa Ser Asn Pro Leu Cys Pro Xaa Glu Thr Gln
   130
Glu Gly
145
```



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<210> 437
 <211> 110
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -20..-1
 <400> 437
 Met Xaa Leu Met Val Leu Val Phe Thr Ile Gly Leu Thr Leu Leu Leu
                     -15
                                         -10
 Gly Xaa Gln Ala Met Pro Ala Asn Arg Leu Ser Cys Tyr Arg Lys Ile
 Leu Lys Asp His Asn Cys His Asn Leu Pro Glu Gly Val Ala Asp Leu
                             20
 Thr Gln Ile Asp Val Asn Val Gln Asp His Phe Trp Asp Gly Lys Gly
                         35
 Cys Glu Met Ile Cys Tyr Cys Asn Phe Lys Arg Ile Ala Leu Leu Pro
                     50
Lys Arg Arg Phe Leu Trp Thr Lys Asp Leu Phe Arg Asp Ser Leu Gln
                65
                                     70
 Gln Ser Met Arg Ile Phe Met Tyr Ser Gly Glu His His Ser
                                 85
<210> 438
<211> 71
 <212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -15..-1
<400> 438
Met Lys Leu Leu Thr His Asn Leu Leu Ser Ser His Val Arg Gly Val
                    -10
                                         -5
Gly Ser Arg Gly Phe Pro Leu Arg Leu Gln Ala Thr Glu Val Arg Ile
                                 10
                                                     15
Cys Pro Val Glu Phe Asn Pro Asn Phe Val Ala Arg Met Ile Pro Lys
                            25
Val Glu Trp Ser Ala Phe Leu Glu Ala Xaa Asp Asn Leu Arg Leu Ile
Gln Val Pro Arg Arg Ala Gly
50
<210> 439
<211> 99
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -24..-1
Met Lys Ser Ala Lys Leu Gly Phe Leu Leu Arg Phe Phe Ile Phe Cys
```

-15

-20

<210> 440



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      Ser
      Leu
      Asn
      Leu
      Leu
      Leu
      Gly
      Val
      Asn
      Lys
      Ile
      Ala
      Glu
      Lys

      Ile
      Cys
      Gly
      Asp
      Leu
      Lys
      Asp
      Pro
      Cys
      Lys
      Leu
      Asp
      Met
      Asn
      Phe
      Gly

      Ile
      Cys
      Gly
      Asp
      Leu
      Lys
      Lys
      Lys
      Leu
      Asp
      Phe
      Gly
      Asp
      A
```

```
<211> 169
  <212> PRT
  <213> Homo sapiens
. <220>
 <221> SIGNAL
 <222> -25..-1
 <400> 440
 Met Arg Lys Pro Ala Ala Gly Phe Leu Pro Ser Leu Leu Lys Val Leu
                     -20
                                          -15
 Leu Leu Pro Leu Ala Pro Ala Ala Ala Gln Asp Ser Thr Gln Ala Ser
                 - 5
 Thr Pro Gly Ser Pro Leu Ser Pro Thr Glu Tyr Gln Arg Phe Phe Ala
 Leu Leu Thr Pro Thr Trp Lys Ala Glu Thr Thr Cys Arg Leu Arg Ala
                         30
 Thr His Gly Cys Arg Asn Pro Thr Leu Val Gln Leu Asp Gln Tyr Glu
                                         50
 Asn His Gly Leu Val Pro Asp Gly Ala Val Cys Ser Asn Leu Pro Tyr
                                     65
 Ala Ser Trp Phe Glu Ser Phe Cys Gln Phe Thr His Tyr Arg Cys Ser
                                 80
 Asn His Val Tyr Tyr Ala Lys Arg Val Leu Cys Ser Gln Pro Val Ser
                             95
 Ile Leu Ser Pro Asn Thr Leu Lys Glu Ile Glu Xaa Ser Ala Glu Val
                        110
 Ser Pro Thr Thr Asp Asp Leu Pro His Leu Thr Pro Leu His Ser Asp
                     125
                                                             135
 Arg Thr Pro Asp Leu Pro Ala Leu Ala
                 140
```

```
<210> 441
<211> 167
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -76..-1
<400> 441
Met Gly Asp Tyr Leu Leu Arg Gly Tyr Arg Met Leu Gly Glu Thr Cys
-75
-70
```



Ala Asp Cys Gly Thr Ile Leu Leu Gln Asp Lys Gln Arg Lys Ile Tyr -55 -50 Cys Val Ala Cys Gln Glu Leu Asp Ser Asp Val Asp Lys Asp Asn Pro -40 -35 Ala Leu Asn Ala Gln Ala Ala Leu Ser Gln Ala Arg Glu His Gln Leu Ala Ser Ala Ser Glu Leu Pro Leu Gly Ser Arg Pro Ala Pro Gln Pro Pro Val Pro Arg Pro Glu His Cys Glu Gly Ala Ala Ala Gly Leu Lys 10 15 Ala Ala Gln Gly Pro Pro Ala Pro Ala Val Pro Pro Asn Thr Xaa Val 25 30 Met Ala Cys Thr Gln Thr Ala Leu Leu Gln Lys Leu Thr Trp Ala Ser 45 Ala Glu Leu Gly Ser Xaa Thr Ser Xaa Gly Lys Xaa Ala Ser Ser Cys 60 Val Ala Leu Ser Ala His Val Arg Arg Pro Cys Ala Ala Cys Ser Ser 75 Tyr Ser Thr Lys Arg Ser Pro 85

<210> 442

<211> 70

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -15..-1

<400> 442

Xaa Leu Ser Lys Arg Asp 50 55

<210> 443

<211> 381

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -33..-1

<400> 443

 Met
 Ser
 Trp
 Thr
 Val
 Pro
 Val
 Arg
 Ala
 Ser
 Gln
 Arg
 Val
 Ser
 Ser

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Lys Met Ala Thr Val Lys Ser Glu Leu Ile Glu Arg Phe Thr Ser Glu
                                     25
  Lys Pro Val His His Ser Lys Val Ser Ile Ile Gly Thr Gly Ser Val
                                  40
  Gly Met Ala Cys Ala Ile Ser Ile Leu Leu Lys Gly Leu Ser Asp Glu
                             55
  Leu Ala Leu Val Asp Leu Asp Glu Xaa Lys Leu Lys Gly Glu Thr Met
                          70
  Asp Leu Gln His Gly Ser Pro Phe Thr Lys Met Pro Asn Ile Val Cys
                     85
  Ser Lys Xaa Tyr Phe Val Thr Ala Asn Ser Asn Leu Val Ile Ile Thr
                 100
                                     105
  Ala Gly Ala Arg Gln Xaa Lys Gly Glu Thr Arg Leu Asn Leu Xaa Gln
                                 120
  Arg Asn Val Ala Ile Phe Lys Leu Met Ile Ser Ser Ile Val Gln Tyr
                             135
  Ser Pro His Cys Lys Leu Ile Ile Val Ser Asn Pro Val Asp Ile Leu
                         150
                                             155
  Thr Tyr Val Ala Trp Lys Leu Ser Ala Phe Pro Lys Asn Arg Ile Ile
                     165
                                         170
. Gly Ser Gly Cys Asn Leu Ile Xaa Ala Arg Phe Arg Phe Leu Ile Gly
                 180
                                     185
 Gln Lys Leu Gly Ile His Ser Glu Ser Cys His Gly Trp Ile Leu Gly
             195
                                 200
 Glu His Gly Asp Ser Ser Val Pro Val Trp Ser Gly Val Asn Ile Ala
         210
                             215
 Gly Val Pro Leu Lys Asp Leu Asn Ser Asp Ile Gly Thr Asp Lys Asp
                         230
                                             235
 Pro Glu Gln Trp Lys Asn Val His Lys Glu Val Thr Ala Thr Ala Tyr
                     245
                                         250
 Glu Ile Ile Lys Met Lys Gly Tyr Thr Ser Trp Ala Ile Gly Leu Ser
                 260
                                     265
 Val Ala Asp Leu Thr Glu Ser Ile Leu Lys Asn Leu Arg Arg Ile His
             275
                                 280
 Pro Val Ser Thr Ile Thr Lys Gly Leu Tyr Gly Ile Xaa Glu Glu Val
                             295
 Phe Leu Ser Ile Pro Cys Ile Leu Gly Glu Asn Gly Ile Thr Asn Leu
                        310
 Ile Lys Ile Lys Leu Thr Pro Glu Glu Glu Ala His Leu Lys Lys Ser
                    325
 Ala Lys Thr Leu Trp Glu Ile Gln Asn Lys Leu Lys Leu
                 340
```

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<210> 444
<211> 39
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -14.:-1
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<210> 445
<211> 50
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 445
Met Val Leu Thr Thr Leu Pro Leu Pro Ser Ala Asn Ser Pro Val Asn
    -35
                     -30
Met Pro Thr Thr Gly Pro Asn Ser Leu Ser Tyr Ala Ser Ser Ala Leu
                        -15
Ser Pro Cys Leu Thr Ala Pro Lys Ser Pro Arg Leu Ala Met Met Pro
                   1
Asp Asn
<210> 446
<211> 51
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 446
Met Thr Pro Trp Cys Leu Ala Cys Leu Gly Arg Arg Pro Leu Ala Ser
                       -20
                                           -15
Leu Gln Trp Ser Leu Thr Leu Ala Trp Cys Gly Ser Gly Ser His Trp
                   -5
                                        ٦
Thr Glu Arg Pro Xaa Gln Xaa Ser Pro Trp Xaa Ser Leu Ser Ala Thr
           10
                                15
Thr Arg Gly
        25
<210> 447
<211> 242
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -30..-1
<400> 447
Met Gly Glu Ala Ser Pro Pro Ala Pro Ala Arg Arg His Leu Leu Val
                    -25
                                        -20
Leu Leu Leu Leu Ser Thr Leu Val Ile Pro Ser Ala Ala Pro
                -10
                                    -5
Ile His Asp Ala Asp Ala Gln Glu Ser Ser Leu Gly Leu Thr Gly Leu
                            10
Gln Ser Leu Leu Gln Gly Phe Ser Arg Leu Phe Leu Lys Gly Asn Leu
                        25
```

Leu Arg Gly Ile Asp Ser Leu Phe Ser Ala Pro Met Asp Phe Arg Gly





```
35
                    40
                                        45
Leu Pro Gly Asn Tyr His Lys Glu Glu Asn Gln Glu His Gln Leu Gly
                55
                                    60
Asn Asn Thr Leu Ser Ser His Leu Gln Ile Asp Lys Met Thr Asp Asn
                                75
Lys Thr Gly Glu Val Leu Ile Ser Glu Asn Val Val Ala Ser Ile Gln
                            90
Pro Xaa Glu Gly Xaa Phe Glu Gly Asp Leu Lys Val Pro Arg Met Glu
                       105
                                            110
Glu Lys Glu Ala Leu Val Pro Xaa Gln Lys Ala Thr Asp Ser Phe His
                    120
                                        125
Thr Glu Leu His Pro Arg Val Ala Phe Trp Ile Ile Lys Leu Pro Arg
               135
                                    140
Arg Arg Ser His Gln Asp Ala Leu Glu Gly Gly His Trp Leu Xaa Glu
                               155
Lys Arg His Arg Leu Gln Ala Ile Arg Asp Gly Leu Arg Lys Gly Thr
                           170
His Lys Asp Xaa Leu Xaa Xaa Gly Thr Glu Ser Ser His Ser Arg
                       185
                                           190
Leu Ser Pro Arg Lys Xaa His Leu Leu Tyr Ile Leu Xaa Pro Ser Arg
                   200
Gln Leu
```

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<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -60..-1
<400> 448
Met Gly Ser Lys Cys Cys Lys Gly Gly Pro Asp Glu Asp Ala Val Glu
                   -55
                                       -50
Arg Gln Arg Arg Gln Lys Leu Leu Leu Ala Gln Leu His His Arg Lys
               -40
                                   -35
Arg Val Lys Ala Ala Gly Gln Ile Gln Ala Trp Trp Arg Gly Val Leu
           -25
                               -20
Val Arg Arg Thr Leu Leu Val Ala Ala Leu Arg Ala Trp Met Ile Gln
        -10
                           - 5
Cys Trp Trp Arg Thr Leu Val Gln Arg Arg Ile Arg Gln Arg Arg Gln
Ala Leu Leu Gly Val Tyr Val Ile Gln Glu Gln Ala Ala Val Lys Leu
                                  30
Gln Ser Cys Ile Arg Met Trp Gln Cys Arg Gln Cys Tyr Arg Gln Met
                               45
Cys Asn Ala Leu Cys Leu Phe Gln Val Pro Lys Ser Ser Leu Ala Phe
                           60
Gln Thr Asp Gly Phe Leu Gln Val Gln Tyr Ala Ile Pro Ser Lys Gln
75
Pro Glu Phe His Ile Glu Ile Leu Ser Ile
```

<210> 449 <211> 89 <212> PRT <213> Homo sapiens

<210> 448 <211> 154



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<220>
<221> SIGNAL
<222> -61..-1
<400> 449
Met Asn Ala Ala Ile Asn Thr Gly Pro Ala Pro Ala Val Thr Lys Thr
                               -50
                   -55
Glu Thr Glu Val Gln Asn Pro Asp Val Leu Trp Asp Leu Asp Ile Pro
                   -40
                                      -35
Glu Ala Arg Ser His Ala Asp Gln Asp Ser Asn Pro Lys Ala Glu Ala
               -25
                                  -20
Leu Leu Pro Cys Asn Leu His Cys Ser Trp Leu His Ser Ser Pro Arg
           -10
                   -5
Pro Asp Pro His Ser His Phe Pro Ser Xaa Arg Arg Cys Pro Leu Pro
                   10
His Pro Cys Ala Thr Tyr Pro Pro Xaa
                  25
<210> 450
<211> 73
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 450
Met Arg Met Ser Leu Ala Gln Arg Val Leu Leu Thr Trp Leu Phe Thr
                       -20
                                          -15
Leu Leu Phe Leu Ile Met Leu Val Leu Lys Leu Asp Glu Lys Ala Pro
                   - 5
Trp Asn Trp Phe Leu Ile Phe Ile Pro Val Trp Ile Phe Asp Thr Ile
          10
                              15
                                                  20
Leu Leu Val Leu Leu Ile Val Lys Met Ala Gly Arg Cys Lys Ser Gly
                          30
Phe Asp Leu Asp Met Asp His Thr Ile
   40
<210> 451
<211> 54
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
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<222> -34..-1 <400> 451 Met Ile Pro Leu Ile Ser His Leu Ala Glu Ala Ala Pro Pro Thr Ser -30 -25 Trp Ser Leu Ile Ser Ser Val Leu Asn Val Gly His Leu Leu Phe Ser -10 - 5 Ser Ala Cys Ser Val Ser Leu Glu Ala Leu Ser Thr Arg Asn Ile Lys Ala Ile Ile Leu Met Lys 15 20



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<210> 452
<211> 121
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -38..-1
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<210> 453 <211> 166 <212> PRT

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<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 453
Met Ser Thr Val Gly Leu Phe His Phe Pro Thr Pro Leu Thr Arg Ile
                            -30
Cys Pro Ala Pro Trp Gly Leu Arg Leu Trp Glu Lys Leu Thr Leu Leu
                        -15
                                            -10
Ser Pro Gly Ile Ala Val Thr Pro Val Gln Met Ala Gly Lys Lys Asp
Tyr Pro Ala Leu Leu Ser Leu Asp Glu Asn Glu Leu Glu Glu Gln Phe
Val Lys Gly His Gly Pro Gly Gly Gln Ala Thr Asn Lys Thr Ser Asn
        30
Cys Val Val Leu Lys Xaa Ile Pro Ser Gly Ile Val Val Lys Cys His
Gln Thr Arg Ser Val Asp Gln Asn Arg Lys Leu Ala Arg Lys Ile Leu
                                        70
Gln Glu Lys Val Xaa Val Phe Tyr Asn Gly Glu Asn Ser Pro Val His
                                    85
Lys Glu Lys Arg Glu Ala Ala Lys Lys Gln Glu Arg Lys Lys Arg
                               100
Ala Lys Glu Thr Leu Glu Lys Lys Xaa Leu Lys Xaa Leu Trp Glu
        110
                            115
```



Ser Ser Lys Lys Val His 125

<210> 454
<211> 180
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1

<400> 454 Met Gly Ile Gln Thr Ser Pro Val Leu Leu Ala Ser Leu Gly Val Gly -20 -15 Leu Val Thr Leu Leu Gly Leu Ala Val Gly Ser Tyr Leu Val Arg Arg - 5 Ser Arg Arg Pro Gln Val Thr Leu Leu Asp Pro Asn Glu Lys Tyr Leu 10 15 Leu Arg Leu Leu Asp Lys Thr Thr Val Ser His Asn Thr Lys Arg Phe 30 Arg Phe Ala Leu Pro Thr Ala His His Thr Leu Gly Leu Pro Val Gly 45 Lys His Ile Tyr Leu Ser Thr Arg Ile Asp Gly Ser Leu Val Ile Arg 60 Pro Tyr Thr Pro Val Thr Ser Asp Glu Asp Gln Gly Tyr Val Asp Leu 80 Val Xaa Lys Val Tyr Leu Lys Gly Val His Pro Lys Phe Pro Glu Gly 95 Gly Lys Met Ser Xaa Tyr Leu Asp Xaa Leu Lys Val Gly Asp Xaa Val , 110 115 Glu Phe Xaa Gly Pro Ser Gly Leu Leu Thr Tyr Thr Gly Lys Gly His 125 130

Phe Asn Ile Gln Pro Asn Lys Asn Leu His Gln Asn Pro Glu Trp Arg

140

<210> 455
<211> 91
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -64..-1
<400> 455

Arg Asn Trp Glu

Met Thr Pro Arg Ile Leu Ser Glu Val Gln Phe Ser Ala Phe Cys Pro
-60 -55 -50

Tyr Trp Thr Ile Ala Arg Ile Leu Glu Arg Val Gly Ser Ala Cys Phe
-45 -40 -35

Arg Leu Glu Leu Cys Ala Ala Ile Val Gly Tyr Phe Val Leu Asp Val
-30 -25 -20

Arg Thr Phe Leu Phe Ile Val Val Cys Val Ile Cys Val Thr Leu Asn
-15 -10 -5

Phe Pro Arg Phe Tyr Phe Leu Cys Leu Ser Ser Leu Thr Ala Phe Gly
1 5 10 15

Thr Pro Pro Ile Gly Val His Ile Pro Ser Pro

25

20

<210> 456

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<211> 257
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 456
Met Arg Arg Ile Ser Leu Thr Ser Ser Pro Val Arg Leu Leu Xaa
                                -15
Leu Leu Leu Leu Ile Ala Leu Glu Ile Met Val Gly Gly His Ser
Leu Cys Phe Asn Phe Thr Ile Lys Ser Leu Ser Arg Pro Gly Gln Pro
                    15
Trp Cys Glu Ala His Val Phe Leu Asn Lys Asn Leu Phe Leu Gln Tyr
Asn Ser Asp Asn Asn Met Val Lys Pro Leu Gly Leu Leu Gly Lys Lys
                                50
Val Tyr Ala Thr Ser Thr Trp Gly Glu Leu Thr Gln Thr Leu Gly Glu
Val Gly Arg Asp Leu Arg Met Leu Leu Cys Asp Ile Lys Pro Gln Ile
Lys Thr Ser Asp Pro Ser Thr Leu Gln Val Xaa Xaa Phe Cys Gln Arg
                                        100
Glu Ala Glu Arg Cys Thr Gly Ala Ser Trp Gln Phe Ala Thr Asn Gly
                110
                                    115
Glu Lys Ser Leu Leu Phe Asp Ala Met Asn Met Thr Trp Thr Val Ile
            125
                                130
Asn His Glu Ala Ser Xaa Ile Lys Glu Thr Trp Lys Lys Asp Arg Xaa
                            145
Leu Glu Xaa Tyr Phe Arg Lys Leu Ser Lys Gly Asp Cys Asp His Trp
                        160
Leu Arg Glu Phe Leu Gly His Trp Glu Ala Met Pro Xaa Pro Xaa Val
                    175
                                        180
Ser Pro Xaa Asn Ala Ser Xaa Ile His Trp Ser Ser Ser Xaa Leu Pro
                190
                                    195
Xaa Xaa Trp Ile Ile Leu Gly Ala Phe Ile Leu Leu Xaa Leu Met Gly
```

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<210> 457
<211> 193
<213> Homo sapiens
```

210 Ile Val Leu Ile Cys Val Trp Trp Gln Asn Gly Xaa Xaa Ser Thr Xaa 225

<220> <221> SIGNAL <222> -60..-1

Xaa

205

<400> 457 Met Cys Pro Ser Leu Glu Glu Ala Pro Ser Val Lys Gly Thr Leu Pro -60 -50



Cys Ser Gly Gln Gln Pro Phe Pro Phe Gly Ala Ser Asn Ile Pro -35 Leu Leu Leu Gly Arg Ser Arg Lys Val Ala Arg Gly Ala Pro Val Leu -25 -20 Trp Pro Phe Leu Thr Trp Ile Asn Pro Ala Leu Ser Ile Cys Asp Pro -5 Leu Gly Ser Cys Gly Trp Xaa Cys His Thr Ala Gln Val Pro Ala Pro 10 15 Leu Gln Leu Pro Thr Ala Cys Pro Pro Leu Pro His Gly Thr Arg Ala 25 30 Val Gly Pro Thr Pro Gly Leu Leu Pro Glu Ala Ala Pro Xaa Thr 45 Xaa Gly Ala Leu Ser Ser Arg Ser Arg His Trp Ser Cys Ser Ile Val 60 Xaa Cys Leu His Leu His Xaa Leu Leu Ser Val Glu Thr Arg Xaa Phe 75 Xaa Lys His Leu Leu Val Leu Leu Val Ala Val Ala His Ser Val Leu 95 Glu Pro Pro Ala Leu Val Pro Asn Val Gln Cys Glu Met Cys Thr His 110 Ser Gly Pro Arg Asp Leu Glu Ala Ala Val Val Ser Pro Ala Pro Trp 125 Glu

<210> 458 <211> 107 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -28..-1

<400> 458 Met Val Leu Thr Leu Gly Glu Ser Trp Pro Val Leu Val Gly Arg Arg -25 -20 Phe Leu Ser Leu Ser Ala Ala Asp Gly Ser Asp Gly Ser His Asp Ser -5 Trp Asp Val Glu Arg Val Ala Glu Trp Pro Trp Leu Ser Gly Thr Ile 10 Arg Ala Val Ser His Thr Asp Val Thr Lys Lys Asp Leu Lys Val Cys 30 Val Glu Phe Xaa Gly Glu Ser Trp Arg Lys Arg Arg Trp Ile Glu Val 45 Tyr Ser Leu Leu Arg Lys Ala Phe Leu Val Lys His Asn Leu Val Leu 60 Ala Glu Arg Lys Ser Pro Glu Ile Ser Trp Gly

<210> 459 <211> 121 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -13..-1



```
<400> 459
Met Leu Val Leu Arg Ser Ala Leu Thr Arg Ala Leu Ala Ser Arg Thr
            -10
Leu Ala Pro Gln Met Cys Ser Ser Phe Ala Thr Gly Pro Arg Gln Tyr
                        10
Asp Gly Ile Phe Tyr Glu Phe Arg Ser Tyr Tyr Leu Lys Pro Ser Lys
                    25
                                        30
Met Asn Glu Phe Leu Glu Asn Phe Glu Lys Asn Ala Gln Leu Arg Thr
               40
                                   45
Ala His Ser Glu Leu Val Gly Tyr Trp Ser Val Xaa Phe Gly Gly Arg
                               60
Met Xaa Thr Val Phe His Ile Trp Lys Tyr Asp Asn Phe Ala His Arg
                           75
Thr Glu Phe Gln Lys Ala Leu Ala Lys Asp Lys Glu Trp Gln Glu Gln
                       90
Phe Leu Ile Pro Asn Leu Ala Leu Asn
```

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<211> 109
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -13..-1
<400> 461
Met Cys Leu Leu Thr Ala Leu Val Thr Gln Val Ile Ser Leu Arg Lys
          -10
                             -5
Asn Ala Glu Arg Thr Cys Leu Cys Lys Arg Arg Trp Pro Trp Xaa Pro
Ser Pro Arg Ile Tyr Cys Ser Ser Thr Pro Cys Asp Ser Lys Phe Pro
                 25
Thr Val Tyr Ser Ser Ala Pro Phe His Ala Pro Leu Pro Val Gln Asn
Ser Leu Trp Gly His Pro Leu His Gly Cys Ser Trp Gln Cys His His
                             60
Pro Gln Gly Gln Asn Leu Gln Pro Ala Ser Leu Xaa Thr His Leu Ser
                         75
Lys Pro Lys Arg His Phe Xaa Lys Lys Xaa Cys Gln Ala
```

<210> 461

85

90

95

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<210> 462
<211> 143
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -41..-1
<400> 462
Met Ala Thr Ala Thr Glu Gln Trp Val Leu Val Glu Met Val Gln Ala
                        -35
                                             -30
Leu Tyr Glu Ala Pro Ala Tyr His Leu Ile Leu Glu Gly Ile Leu Ile
                    -20
                                         -15
Leu Trp Ile Ile Arg Leu Leu Phe Ser Lys Thr Tyr Lys Leu Gln Glu
                -5
Arg Ser Asp Leu Thr Val Lys Glu Lys Glu Glu Leu Ile Glu Glu Trp
        10
                            15
Gln Pro Glu Pro Leu Val Pro Pro Val Pro Lys Asp His Pro Ala Leu
                        30
                                             35
Asn Tyr Asn Ile Val Ser Gly Pro Pro Ser His Lys Thr Val Val Asn
Gly Lys Glu Cys Ile Asn Phe Ala Ser Phe Asn Phe Leu Gly Leu Leu
                                    65
Asp Asn Pro Arg Val Lys Ala Ala Ala Leu Ala Ser Leu Lys Lys Tyr
            75
                                80
Gly Val Gly Thr Cys Gly Pro Cys Gly Phe Tyr Gly Thr Phe Glu
                            95
<210> 463
<211> 232
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -30..-1
<400> 463
Met Ala Ala Thr Ser Gly Thr Asp Glu Pro Val Ser Gly Glu Leu Val
                    -25
                                         -20
Ser Val Ala His Ala Leu Ser Leu Pro Ala Glu Ser Tyr Gly Asn Xaa
                -10
Xaa Asp Ile Glu Met Ala Trp Ala Met Arg Ala Met Gln His Ala Glu
```

Val Tyr Tyr Lys Leu Ile Ser Ser Val Asp Pro Gln Phe Leu Lys Leu

Thr Lys Val Asp Asp Gln Ile Tyr Ser Glu Phe Arg Lys Asn Phe Glu

Thr Leu Arg Ile Asp Val Leu Xaa Pro Glu Xaa Leu Lys Ser Glu Ser

Ala Lys Glu Pro Pro Gly Tyr Asn Ser Leu Pro Leu Lys Leu Leu Gly
70 75 80

Thr Gly Lys Ala Ile Thr Lys Leu Phe Ile Ser Val Phe Arg Thr Lys
85 90 95

Lys Glu Arg Lys Glu Ser Thr Met Glu Glu Lys Lys Glu Leu Thr Val

30

45

60

25



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100
                       105
                                           110
Glu Lys Lys Arg Thr Pro Arg Met Glu Glu Arg Lys Glu Leu Ile Val
           120
                                       125
Glu Lys Lys Lys Arg Lys Glu Ser Thr Glu Lys Thr Lys Leu Thr Lys
               135
Glu Glu Lys Lys Gly Lys Lys Leu Thr Lys Lys Ser Thr Lys Val Val
                               155
                                                  160
Lys Lys Leu Cys Lys Val Tyr Arg Glu Gln His Ser Arg Ser Tyr Asp
                           170
                                           175
Ser Ile Glu Thr Thr Ser Thr Thr Val Leu Leu Ala Gln Thr Pro Leu
                       185
Val Lys Cys Lys Phe Leu Tyr Asn
```

<210> 464
<211> 61
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 464
Met Thr Phe Arg His Gln Asp Asn Ser

<210> 466 <211> 215 <212> PRT <213> Homo sapiens

<220>



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<221> SIGNAL <222> -54..-1
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<400> 466 Met Asn Xaa Tyr Ala Ser Pro Phe Asn Xaa Gln Leu Xaa Tyr Leu Xaa -45 -50 Leu Ser Arg Phe Glu Cys Val His Arg Asp Gly Arg Val Ile Thr Leu -30 Ser Tyr Gln Glu Gln Glu Leu Gln Asp Phe Leu Leu Ser Gln Met Ser -15 -10 Gln His Gln Val His Ala Val Gln Gln Leu Ala Lys Val Met Gly Trp Gln Val Leu Ser Phe Ser Asn His Val Gly Leu Gly Pro Ile Glu Ser Xaa Gly Asn Ala Ser Ala Ile Thr Val Ala Pro Gln Val Val Thr Met 35 Leu Phe Gln Phe Val Met Asp Leu Lys Val Ala Ala Arg Leu Trp Phe Ser Phe Leu Val Thr Asn Val Lys Thr Phe Gln Lys Val Met Phe Tyr 65 Lys Ile Thr Asn Gly Val Ile Phe Val Gly His Ser Lys Lys Phe Ser 80 85 Gly Ile Lys Trp Lys Val Xaa Ile Leu Phe Ile Lys Trp Xaa Cys Leu 95 100 Cys Leu His Leu Ala Leu Val Tyr Tyr Asp Phe Phe Gln Met Phe Pro 110 115 120 Lys Xaa Val Ser Xaa Asn Phe Asp Leu Lys Cys Leu Gln Ile Asn Tyr 130 135 Lys His Lys Glu Glu Ile Thr Ser Lys Arg Val Leu Phe Leu Lys Ile

145

Ile Ile Arg Lys Cys Phe Ile

<210> 468 <211> 85 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -24..-1 <400> 468





<212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -43..-1 <400> 470 Met Thr Pro Gln Tyr Leu Pro His Gly Gly Lys Tyr Gln Val Leu Gly -35 Asp Tyr Ser Leu Ala Val Val Phe Pro Leu His Phe Ser Asp Leu Ile -20 -15 Ser Val Leu Tyr Leu Ile Pro Lys Thr Leu Thr Thr Asn Thr Ala Val -5 1 5 Lys-His-Ser Ile-Gln Lys-Asn-Cys-Met-Xaa-Leu-Val-Leu-Gly-Lys-Leu----10 15 Leu Ser Gln

<210> 471 <211> 63 <212> PRT <213> Homo sapiens

<210> 470 <211> 67

<213> Homo sapiens



```
<220>
<221> SIGNAL
<222> -15..-1
<400> 471
Met Gly Ile Leu Ser Thr Val Thr Ala Leu Thr Phe Ala Arg Ala Leu
                    -10
Asp Gly Cys Arg Asn Gly Ile Ala His Pro Ala Ser Glu Lys His Arg
                                10
Leu Glu Lys Cys Arg Glu Leu Glu Ser Ser His Ser Ala Pro Gly Ser
                            25
Thr Gln His Arg Arg Lys Thr Thr Arg Arg Asn Tyr Ser Ser Ala
<210> 472
<211> 179
<212> PRT
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<220> <221> SIGNAL <222> -58..-1 <400> 472 Met Ser Thr Gly Gln Leu Tyr Arg Met Glu Asp Ile Gly Arg Phe His -55 -50 Ser Gln Gln Pro Gly Ser Leu Thr Pro Ser Ser Pro Thr Val Gly Glu -35 Ile Ile Tyr Asn Asn Thr Arg Asn Thr Leu Gly Trp Ile Gly Gly Ile -20 Leu Met Gly Ser Phe Gln Gly Thr Ile Ala Gly Gln Gly Thr Gly Ala - 5 Thr Ser Ile Ser Glu Leu Cys Lys Gly Gln Glu Leu Glu Pro Ser Gly 15 Ala Gly Leu Thr Val Ala Pro Pro Gln Ala Val Ser Leu Gln Gly Ile 30 Tyr Thr Leu Pro Trp Leu Leu Gln Leu Phe His Ser Thr Ala Leu Xaa 45 Xaa Xaa Gln Gln Pro Asn Gly Ser Leu Ser Leu Asn Ile Ser Ser Ser 60 65 His Ala Pro Xaa Pro Xaa Thr Cys Thr Leu Glu Pro Gly Val Asp Pro 75 80 Thr Arg Xaa Val Cys Ile Asn Pro His Pro Pro Pro Pro Ile Leu Lys 95 Xaa Pro Leu Ser Pro Tyr Pro Lys Pro Gln Leu Gly Thr His Ala Gly 105 Gln Val Asn

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<210> 473
<211> 238
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
```

<222> -71..-1



-25

```
<400> 473
Met Xaa Xaa Phe Thr Asp Pro Ser Ser Val Asn Glu Lys Lys Arg Arg
                        -65
Glu Arg Glu Glu Arg Gln Asn Ile Val Leu Trp Arg Gln Pro Leu Ile
                    -50
                                        -45
Thr Leu Gln Tyr Phe Ser Leu Glu Ile Leu Val Ile Leu Lys Glu Trp
                -35
                                    -30
Thr Ser Lys Leu Trp His Arg Gln Ser Ile Val Val Ser Phe Leu Leu
                                -15
Leu Leu Ala Gly Leu Ile Ala Thr Tyr Tyr Val Glu Gly Val His Gln
                            1-
                                            -5-
Gln Tyr Val Gln Arg Ile Glu Lys Gln Phe Leu Leu Tyr Ala Tyr Trp
                    15
                                        20
Ile Gly Leu Gly Ile Leu Ser Ser Val Gly Leu Gly Thr Gly Leu His
                                    35
Thr Phe Leu Leu Tyr Leu Gly Pro His Ile Ala Ser Val Thr Leu Ala
                                50
Ala Tyr Glu Cys Asn Ser Val Asn Phe Pro Glu Pro Pro Tyr Pro Asp
                            65
Gln Ile Ile Cys Pro Asp Glu Glu Gly Thr Glu Gly Thr Ile Ser Leu
                        80
Trp Ser Ile Ile Ser Lys Val Arg Ile Glu Ala Cys Met Trp Gly Ile
                    95
                                        100
Gly Thr Ala Ile Gly Glu Leu Pro Pro Tyr Phe Met Ala Arg Ala Ala
                110
                                    115
Arg Leu Ser Gly Ala Glu Pro Asp Asp Glu Glu Tyr Gln Glu Phe Glu
           125
                                130
Glu Met Leu Glu His Ala Glu Ser Ala Gln Val Arg Thr Val Gly Ile
                            145
Glu Asn Arg Thr Leu Tyr Phe Phe Leu Lys Arg Leu Leu Arg
                        160
```

<210> 474
<211> 178
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 474
Met Glu Arg Gln Ser Arg Val Met Ser Glu Lys Asp Glu Tyr Gln Phe

-35

Gln His Gln Gly Ala Val Glu Leu Leu Val Phe Asn Phe Leu Leu Ile
-20 -15 -10

Leu Thr Ile Leu Thr Ile Trp Leu Phe Lys Asn His Arg Phe Arg Phe
-5 -10

Leu His Glu Thr Gly Gly Ala Met Val Tyr Gly Leu Xaa Met Gly Leu
15 -20 -25

Ile Leu Xaa Tyr Ala Thr Ala Pro Thr Asp Ile Glu Ser Gly Xaa Val
30 35 40

Tyr Asp Cys Val Lys Leu Thr Phe Ser Pro Ser Thr Leu Leu Val Asn
45 50 55

Ile Thr Asp Gln Val Tyr Glu Tyr Lys Tyr Lys Arg Glu Ile Ser Gln
60 65 70 75

His Xaa Ile Asn Pro His Xaa Gly Asn Ala Ile Leu Glu Lys Met Thr
80 Phe Asp Pro Xaa Ile Phe Phe Asn Val Leu Leu Pro Pro Ile Ile Phe

-30



```
His Ala Gly Tyr Ser Leu Lys Lys Arg His Phe Phe Gln Asn Leu Gly 110 115 120

Ser Ile Leu Thr Tyr Ala Phe Leu Gly Thr Ala Ile Ser Cys Ile Val 125 130 135

Ile Gly 140
```

```
<210> 475
<211> 96
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 475
Met Ser Met Gln Phe Leu Phe Lys Met Val Ala Leu Cys Cys Cys Leu
                        -15
Trp Lys Ile Ser Gly Cys Glu Glu Val Pro Leu Thr Tyr Asn Leu Leu
Lys Cys Leu Leu Asp Lys Ala His Cys Val Leu Leu Thr Pro Cys Gly
                                20
Tyr Ile Phe Ser Leu Ile Ser Pro Glu Ile Leu Lys Leu Thr Leu Ile
                           35
Thr Leu Xaa Ile Leu Leu Ile Leu Lys Asn Leu His Leu Leu Trp Leu
                    50
Thr Val Ser Ser Xaa Cys Val His Arg Ser Ser Ala Arg Lys Glu Lys
```

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<210> 477
<211> 113
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -27..-1
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<210> 478 <211> 250 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

225

<222> -18..-1 <400> 478 Met Arg Ile Leu Gln Leu Ile Leu Leu Ala Leu Ala Thr Gly Leu Val -15 -10 Gly Gly Glu Thr Arg Ile Ile Lys Gly Phe Glu Cys Lys Pro His Ser Gln Pro Trp Gln Ala Ala Leu Phe Glu Lys Thr Arg Leu Leu Cys Gly 20 25 Ala Thr Leu Ile Ala Pro Arg Trp Leu Leu Thr Ala Ala His Cys Leu 35 40 Lys Pro Arg Tyr Ile Xaa His Leu Gly Gln His Asn Leu Gln Lys Glu 55 Glu Gly Cys Glu Gln Thr Arg Thr Ala Thr Glu Ser Phe Pro His Pro 70 Gly Phe Asn Asn Ser Leu Pro Asn Lys Asp Xaa Xaa Asn Asp Ile Met 85 Leu Val Xaa Met Xaa Ser Pro Val Ser Ile Thr Trp Ala Val Arg Pro 100 Leu Thr Leu Ser Ser Arg Cys Val Thr Ala Gly Thr Ser Cys Leu Ile 115 Ser Gly Trp Gly Ser Thr Ser Ser Pro Gln Leu Arg Leu Pro His Thr 130 Leu Arg Cys Ala Asn Ile Thr Ile Ile Glu His Gln Lys Cys Glu Asn 150 155 Ala-Tyr-Pro Gly Asn Ile Thr Asp Thr Met Val Cys Ala Ser Val Gln 165 170 Glu Gly Gly Lys Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val 180 185 Cys Asn Gln Ser Leu Gln Gly Ile Ile Ser Trp Gly Gln Asp Pro Cys 200 Ala Ile Thr Arg Lys Pro Gly Val Tyr Thr Lys Val Cys Lys Tyr Val 210 215 Asp Trp Ile Gln Glu Thr Met Lys Asn Asn

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<210> 479
<211> 151
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 479
Met Ala Ala Ser Thr Ser Met Val Pro Val Ala Val Thr Ala Ala Val
                        -15
                                            -10
Ala Pro Val Leu Ser Ile Asn Ser Asp Phe Ser Asp Leu Arg Glu Ile
Lys Lys Gln Leu Leu Ile Ala Gly Leu Thr Arg Glu Arg Gly Leu
            15
                                20
Leu His Ser Ser Lys Trp Ser Ala Glu Leu Ala Phe Ser Leu Pro Ala
                            35
Leu Pro Leu Ala Glu Leu Gln Pro Pro Pro Pro Ile Thr Glu Glu Asp
                       50
Ala Gln Asp Met Asp Ala Tyr Thr Leu Ala Lys Ala Tyr Phe Asp Val
                   65
                                        70
Lys Glu Tyr Asp Arg Ala Ala His Phe Leu His Gly Cys Asn Ala Arg
                                    85
Lys Ala Tyr Phe Leu Tyr Met Tyr Ser Arg Tyr Leu Val Arg Ala Ile
                               100
Leu Lys Cys His Ser Ala Phe Ser Glu Thr Ser Ile Phe Arg Thr Asn
       110
                            115
Gly Lys Val Lys Ser Phe Lys
   125
                        130
```

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<210> 480
<211> 239
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -25..-1
<400> 480
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Met Pro Arg Lys Arg Lys Cys Asp Leu Arg Ala Val Arg Val Gly Leu -20 -15 Leu Leu Gly Gly Gly Val Tyr Gly Ser Arg Phe Arg Phe Thr Phe -5 Pro Gly Cys Arg Ala Leu Ser Pro Trp Arg Val Arg Xaa Gln Arg Arg 15 Arg Cys Glu Met Ser Thr Met Phe Ala Asp Thr Leu Leu Ile Val Phe 30 Ile Ser Val Cys Thr Ala Leu Leu Ala Glu Gly Ile Thr Trp Val Leu 45 50 Val Tyr Arg Thr Asp Lys Tyr Lys Arg Leu Lys Ala Glu Val Glu Lys 60 65 Gln Ser Lys Lys Leu Glu Lys Lys Lys Glu Thr Ile Thr Glu Ser Ala 80 Gly Arg Gln Gln Lys Lys Lys Ile Glu Arg Xaa Xaa Xaa Leu Xaa 95



```
Asn Asn Asn Arg Asp Leu Ser Met Val Arg Met Lys Ser Met Phe Ala
                       110
                                           115
Ile Gly Phe Cys Phe Thr Ala Leu Met Gly Met Phe Asn Ser Ile Phe
                    125
                                       130
Asp Gly Arg Val Val Ala Lys Leu Pro Phe Thr Pro Leu Ser Xaa Xaa
                140
                                   145
Xaa Gly Leu Ser His Arg Asn Leu Leu Gly Asp Asp Thr Thr Asp Cys
                               160
Ser Phe Ile Phe Leu Xaa Ile Leu Cys Thr Met Ser Ile Arg Gln Asn
                           175
Ile Gln Lys Ile Leu Gly Leu Ala Pro Ser Arg Ala Ala Thr Lys Gln
                      190
Ala Gly Gly Phe Leu Gly Pro Pro Pro Pro Ser Gly Lys Phe Ser
                   205
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<210> 481 <211> 208 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -92..-1 <400> 481

Met Arg Glu Pro Gln Lys Arg Thr Ala Thr Ile Ala Lys Xaa Xaa Ala -85 Xaa Glu Gly Leu Arg Asp Pro Tyr Gly Arg Leu Cys Gly Ser Glu His -70 Pro Arg Arg Pro Pro Glu Arg Pro Glu Glu Asp Pro Ser Thr Pro Glu -55 -50 Glu Ala Ser Thr Thr Pro Glu Glu Ala Ser Ser Thr Ala Gln Ala Gln -40 -35 Lys Pro Ser Val Pro Arg Ser Asn Phe Gln Gly Thr Lys Lys Ser Leu -20 -15 Leu Met Ser Ile Leu Ala Leu Ile Phe Ile Met Gly Asn Ser Ala Lys -5 Glu Ala Leu Val Trp Lys Val Leu Gly Lys Leu Gly Met Gln Pro Gly 10 Arg Xaa His Ser Ile Phe Gly Asp Pro Lys Lys Ile Val Thr Glu Xaa 25 30 Phe Val Arg Arg Gly Tyr Leu Ile Tyr Xaa Pro Val Pro Arg Xaa Ser 40 45 Pro Val Glu Tyr Xaa Phe Phe Trp Gly Pro Arg Ala His Val Glu Ser 60 Ser Xaa Leu Lys Xaa Xaa His Phe Val Ala Arg Val Arg Asn Arg Cys 75 Ser Lys Asp Trp Pro Cys Asn Tyr Asp Trp Asp Ser Asp Asp Ala 90 95 Glu Val Glu Ala Ile Leu Asn Ser Gly Ala Xaa Gly Tyr Ser Ala Pro 

<210> 482 <211> 86 <212> PRT <213> Homo sapiens

<220>

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PCT/IB98/02122.
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<221> SIGNAL
<222> -39..-1
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WO 99/31236

<400> 482

Met Asn Val Gly Thr Ala His Xaa Xaa Val Asn Pro Asn Thr Arg Val -35 -30 Met Asn Ser Arg Gly Ile Trp Leu Ser Tyr Val Leu Ala Ile Gly Leu -20 -15 Leu His Ile Val Leu Leu Ser Ile Pro Phe Val Ser Val Pro Val Val 1 Trp Thr Leu Thr Asn Leu Ile His Asn Met Gly Met Tyr Ile Phe Leu 10 15 20 His Thr Val Lys Gly Thr Pro Phe Glu Thr Pro Asp Gln Gly Lys Ala

35

30 Arg Leu Leu Thr His Trp 45

<210> 483

<211> 40

<212> PRT

<213> Homo sapiens

<220'>

<221> SIGNAL

<222> -27..-1

<400> 483

Met Arg Thr Leu Phe Gly Ala Val Arg Ala Pro Phe Ser Ser Leu Thr -20 -15

Leu Leu Ile Thr Pro Ser Pro Ser Pro Leu Leu Phe Asp Arg Gly -5

Leu Ser Leu Arg Ser Ala Met Ser

10

<210> 484

<211> 65

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -16..-1

<400> 484

Met Leu Gly Phe Phe Leu Phe Leu Ser Phe Val Leu Met Tyr Asp Gly -10 - 5

Leu Arg Leu Phe Gly Ile Leu Ser Thr Cys Arg Val His His Thr Met 10

Asn Gln Phe Leu Ile Asp Ile Ser Ser Phe Thr Ser Arg Val Lys Lys 25

Lys Ile Phe Leu Phe Tyr Ala Phe Xaa Gly Cys Xaa Phe Gln Ser Ala 40

Thr

<210> 485

<211> 130

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<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -55..-1
<400> 485
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Met Ala Met Trp Asn Arg Pro Xaa Xaa Xaa Leu Pro Gln Gln Pro Leu -50 -45 Xaa Ala Glu Pro Thr Ala Glu Gly Glu Pro His Leu Pro Thr Gly Arg -35 -30 -25 Xaa Xaa Thr Glu Ala Asn Arg Phe Ala Tyr Ala Ala Leu Cys Gly Ile -15 Ser Leu Ser Gln Leu Phe Pro Glu Pro Glu His Ser Ser Phe Cys Thr Glu Phe Met Ala Gly Leu Val Xaa Trp Leu Glu Leu Ser Glu Ala Val 15 20 Leu Pro Thr Met Thr Ala Phe Ala Ser Gly Leu Gly Gly Glu Gly Xaa 35 Xaa Cys Val Cys Ser Asn Phe Thr Glu Gly Pro His Leu Glu Gly Arg

45 50 Pro Asp Gly Asp His Ser Gly Pro Ser Glu Leu Leu Thr Gln Gly Trp 65

Ala Leu 75

<210> 486 <211> 209 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<400> 486

<222> -84..-1

Met Val Asn Phe Pro Gln Lys Ile Ala Gly Glu Leu Tyr Gly Pro Leu -80 -75 Met Leu Val Phe Thr Leu Val Ala Ile Leu Leu His Gly Met Lys Thr -60 -65 Ser Asp Thr Ile Ile Arg Glu Gly Thr Leu Met Gly Thr Ala Ile Gly -45 -40 Thr Cys Phe Gly Tyr Trp Leu Gly Val Ser Ser Phe Ile Tyr Phe Leu -35 -30 -25 Ala Tyr Leu Cys Asn Ala Gln Ile Thr Met Leu Gln Met Leu Ala Leu -15 -10 Leu Gly Tyr Gly Leu Phe Gly His Cys Ile Val Leu Phe Ile Thr Tyr 5 Asn Ile His Leu Arg Ala Leu Phe Tyr Leu Phe Trp Leu Leu Val Gly Gly Leu Ser Thr Leu Arg Met Val Ala Val Leu Val Ser Arg Thr Val Gly Pro Thr Xaa Arg Xaa Leu Leu Cys Gly Thr Leu Ala Ala Leu His 50 Met Leu Phe Leu Leu Tyr Leu His Phe Ala Tyr His Lys Xaa Val Xaa 70 Gly Ile Leu Asp Thr Leu Glu Gly Pro Asn Ile Pro Pro Ile Gln Arg 85

Val Pro Arg Asp Ile Pro Ala Met Leu Pro Ala Ala Arg Leu Pro Thr

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PCT/IB98/02122 ·
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```
95
                             100
                                                 105
Thr Val Leu Asn Ala Thr Ala Lys Ala Val Ala Val Thr Leu Gln Ser
                        115
His
125
<210> 487
<211> 36
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -17..-1
<400> 487
Met Gly Trp Gln Arg Trp Trp Cys Phe His Leu Gln Ala Glu Ala Ser
        -15
                            -10
Ala His Pro Pro Gln Gly Leu Gln Ala Gln Phe Ser Cys Cys Pro Trp
                    5
Val Gly Ile Cys
<210> 488
<211> 44
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -29..-1
<400> 488
Met Met Ser Ser Glu Leu Arg Arg Asn Pro His Phe Leu Lys Ser Asn
                                    -20
Leu Phe Leu Gln Leu Leu Val Ser His Glu Ile Val Cys Ala Thr Glu
                                -5
Thr Val Thr Thr Asn Phe Leu Arg His Glu Lys Ala
   5
                        10
<210> 489
<211> 163
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -52..-1
<400> 489
Met Glu His Tyr Arg Lys Ala Gly Ser Val Glu Leu Pro Ala Pro Ser
       -50
                            ~45
Pro Met Pro Gln Leu Pro Pro Asp Thr Leu Glu Met Arg Val Arg Asp
                        -30
Gly Ser Lys Ile Arg Asn Leu Leu Gly Leu Ala Leu Gly Arg Leu Glu
                    -15
```

Gly Gly Ser Ala Arg His Val Val Phe Ser Gly Ser Gly Arg Ala Ala

-45
-40
-35

Lys Val Ser Gln Gly Pro Leu Phe Asn Val Thr Ser Gly Ser Ser Ser
-30
-25
-25
-20

Pro Val Thr Trp Leu Gly Leu Leu Ser Phe Gln Asn Leu His Cys Phe
-15
-10
-10
-5
1

Pro Asp Leu Pro Thr Glu Met Pro Leu Xaa Ala Lys Gly Xaa Asn Thr

<210> 491 <211> 218 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -50..-1 <400> 491 Met His His Gly Leu Thr Pro Leu Leu Leu Gly Val His Glu Gln Lys -45 -40 Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly -15 -10 -5 Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser Ser Gln Asp Leu Ser Gly Gln Thr Ala Lys Lys Tyr Ala Val Ser Ser 20 25 Arg His Asn Val Ile Cys Gln Leu Leu Ser Asp Tyr Lys Xaa Lys Gln

Xaa Leu Lys Val Ser Ser Glu Asn Ser Asn Pro Xaa Gln Asp Leu Lys



50 55 Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu Lys Gly Ser Glu Asn Ser 70 Gln Pro Glu Glu Met Ser Gln Glu Pro Glu Ile Asn Xaa Gly Gly Asp Arg Lys Val Glu Xaa Xaa Met Lys Lys His Gly Ser Xaa His Met Gly 100 105 Phe Pro Xaa Asn Leu Xaa Asn Gly Ala Thr Ala Asp Asn Gly Asp Asp 120 Gly Leu Ile Pro Pro Xaa Lys Xaa Xaa Thr Pro Glu Ser Xaa Gln Phe 135 Pro Asp Thr Glu Asn Glu Gln Tyr His Arg Asp Phe Ser Gly His Pro 150 Xaa Phe Pro Thr Thr Leu Pro Ile Lys Gln 165

<210> 492 <211> 216 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -15..-1

<400> 492

Met Val Cys Val Leu Val Leu Ala Ala Ala Gly Ala Val Ala Val -10 Phe Leu Ile Leu Arg Ile Trp Val Val Leu Arg Ser Met Asp Val Thr 10 Pro Arg Glu Ser Leu Ser Ile Leu Val Val Ala Gly Ser Gly Gly His Thr Thr Glu Ile Leu Arg Leu Leu Gly Ser Leu Ser Asn Ala Tyr Ser 45 Pro Arg His Tyr Val Ile Ala Asp Thr Asp Glu Met Ser Ala Asn Lys 60 Ile Asn Ser Phe Glu Leu Xaa Arg Xaa Asp Arg Xaa Pro Ser Asn Met 75 Xaa Thr Lys Tyr Tyr Ile His Arg Ile Pro Xaa Ser Arg Glu Val Gln 90 Gln Ser Trp Pro Ser Thr Val Xaa Thr Thr Leu His Ser Met Trp Leu 105 Ser Xaa Pro Leu Ile His Arg Val Lys Pro Xaa Leu Val Leu Cys Asn 120 125 Gly Pro Gly Thr Cys Val Pro Ile Cys Val Ser Ala Leu Leu Gly 135 140 Ile Leu Gly Ile Lys Lys Val Ile Ile Val Tyr Val Glu Ser Ile Cys 155 Arg Val Lys Thr Leu Ser Met Ser Gly Lys Ile Leu Phe His Leu Ser 170 Asn Tyr Phe Ile Val Gln Trp Pro Ala Leu Lys Glu Lys Tyr Pro Lys 185 Ser Val Tyr Leu Gly Arg Ile Val 200

<210> 493 <211> 134 <212> PRT

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<213> Homo sapiens
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<220>

<221> SIGNAL

<222> -19..-1

<400> 493

Met Pro Leu Gly Ala Arg Ile Leu Phe His Gly Val Phe Tyr Ala Gly -15 -10

Gly Phe Ala Ile Val Tyr Tyr Leu Ile Gln Lys Phe His Ser Arg Thr

Leu Tyr Tyr Lys Leu Ala Val Glu Gln Leu Gln Xaa His Pro Glu Ala 15 20

Gln Glu Ala Leu Gly Pro Pro Leu Asn Ile His Tyr Leu Lys Leu Ile 35

Asp Arg Glu Asn Phe Val Asp Ile Val Xaa Ala Lys Leu Lys Ile Pro

Val Ser Gly Ser Lys Ser Glu Gly Leu Leu Tyr Val His Ser Ser Arg

Gly Gly Pro Phe Gln Arg Trp His Leu Asp Glu Val Phe Leu Glu Leu 85

Lys Asp Gly Gln Gln Ile Pro Val Phe Lys Leu Ser Gly Glu Asn Gly 100

Asp Glu Val Lys Lys Glu 110

<210> 494

<211> 85

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -16..-1

<400> 494

Met Ala Val Thr Ala Leu Ala Ala Xaa Thr Trp Leu Gly Val Trp Gly -10

Val Arg Thr Met Gln Ala Arg Gly Phe Gly Ser Asp Gln Ser Glu Asn 10

Val Asp Arg Gly Ala Gly Ser Ile Arg Glu Ala Gly Gly Ala Phe Gly 25

Lys Arg Glu Gln Ala Glu Glu Glu Arg Tyr Phe Arg Ala Gln Ser Thr 40

Glu Gln Leu Ala Xaa Leu Lys Lys Xaa His Glu Glu Glu Ile Val His

His Arg Glu Gly Asp

<210> 495

<211> 292

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -29..-1



<400	0 > 49	95													
Met	His	Gly	Leu	Leu -25	His	Tyr	Leu	Phe	His	Thr	Arg	Asn	His	Thr	
Ile	Val	Leu	His	Leu	Val	Leu	Gln	Gly -5	Met	Val	Tyr	Thr	Glu 1.	Tyr	Thr
_	5			_	_	10			Leu		15				_
Leu 20	Leu	Leu	Pro	Tyr	Leu 25	Leu	Leu	Gly	Val	Asn 30	Leu	Phe	Phe	Phe	Thr
Leu	Thr	Cys	Gly	Thr 40	Asn	Pro	Gly	Ile	Ile 45	Thr	Lys	Ala	Asn	Glu 50	Leu
Leu	Phe	Leu	His 55	Val	Tyr	Glu	Phe	Asp 60	Glu	Xaa	Met	Phe	Pro 65	Lys	Asn
	_	70			_		75	_	Lys			80			
Cys	Xaa 85	Val	Cys	Asn	Trp	Cys 90	Val	His	Arg	Phe	Xaa 95	His	His	Cys	Val
Trp 100	Val	Asn	Asn	Cys	Ile 105	Gly	Ala	Trp	Asn	Ile 110	Arg	Xaa	Phe	Leu	Ile 115
Tyr	Val	Leu	Thr	Leu 120	Thr	Ala	Ser	Ala	Ala 125	Thr	Val	Ala	Ile	Val 130	Ser
Thr	Thr	Phe	Leu 135	Val	His	Leu	Val	Val 140	Met	Ser	Asp	Leu	Tyr 145	Gln	Glu
Thr	Tyr	Ile 150	Asp	Asp	Leu	Gly	His 155	Leu	His	Val	Met	Asp 160	Thr	Val	Phe
Leu	Ile 165	Gln	Tyr	Leu	Phe	Leu 170	Thr	Phe	Pro	Arg	Ile 175	Val	Phe	Met	Leu
Gly 180	Phe	Val	Val	Val	Leu 185	Xaa	Phe	Leu	Leu	Gly 190	Gly	Tyr	Leu	Leu	Phe 195
Val	Leu	Tyr	Leu	Ala 200	Ala	Thr	Asn	Gln	Thr 205	Thr	Asn	Glu	Trp	Tyr 210	Arg
Xaa	Asp	Trp	Ala 215	Trp	Cys	Gln	Arg	Cys 220	Pro	Leu	Val	Ala	Trp 225	Pro	Pro
Ser	Ala	Glu 230	Pro	Gln	Val	His	Arg 235	Asn	Ile	His	Ser	His 240	Gly	Leu	Arg
Xaa	Asn 245	Leu	Gln	Glu	Ile	Phe 250	Leu	Pro	Ala	Phe	Pro 255	Cys	His	Glu	Arg
Lys 260	Гуs	Gln	Glu												

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<210> 496
<211> 122
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -56..-1
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<400> 496 Met Thr Gly Phe Leu Leu Pro Pro Ala Ser Arg Gly Thr Arg Arg Ser -50 -45 Cys Ser Arg Ser Arg Lys Arg Gln Thr Arg Arg Arg Arg Asn Pro Ser -35 -30 Ser Phe Val Ala Ser Cys Pro Thr Leu Leu Pro Phe Ala Cys Val Pro -20 -15 Gly Ala Ser Pro Thr Thr Leu Ala Phe Pro Pro Val Xaa Leu Thr Gly 1 Pro Xaa Thr Asp Gly Ile Pro Phe Ala Leu Xaa Ser Ala Ala Gly Pro 10

20

<210> 497

 Phe Cys Ala Ser Phe Pro Ser Gly Xaa Leu Ser Pro Pro Gly Pro Leu

 25
 30
 35
 40

 Pro Gly Val Arg Gly Leu Pro Leu Pro Ser Val Phe Tyr Ser Cys Gly
 50
 55

 Ala His Pro Lys Val Leu Lys Val Ala Leu
 60
 65

<211> 59 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -28..-1 <400> 497 Met Leu Xaa Leu Ser Arg Ala Thr Lys Xaa Gly Arg Ala Arg Trp Leu -25 -20 Met Pro Val Ile Pro Ala Leu Gln Glu Ala Xaa Ala Gly Gly Ser Arg -10 -5 Gly Gln Glu Phe Glu Thr Ser Leu Ala Asn Met Glu Thr Glu Ala Gly 10 Glu Leu Leu Lys Pro Arg Arg Arg Leu Gln

<210> 498 <211> 99 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -13..-1 <400> 498

<210> 499 <211> 99 <212> PRT <213> Homo sapiens



<220> <221> SIGNAL

<222> -13..-1

<400> 499

Met His Leu Leu Ser Asn Trp Ala Asn Pro Ala Ser Ser Arg Arg Pro
-10 -5 1

Ser Met Ala Ala Ser Gly Thr Ser Trp Ile Ser Ser Thr Leu Ala His 5 10 15

Ser Leu Ser Leu Arg Asp Val Ser Glu Arg Leu Cys Ser Cys Trp Arg 20 25 30 35

Thr Ile Ser Met Gly Pro Cys Ala Arg Gly Ser Pro Met Asn Ser Ser 40 45 50

Gly Val His Arg Lys Ser Ser Arg Leu Phe Tyr Ile Arg Thr Pro Met 55 60 65

Arg Arg Ser Ser Cys His Leu Xaa Cys Gln Val Ile Phe Leu Leu Gly
70 75 80

Arg Gln Leu 85

<210> 500

<211> 108

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -25..-1

<400> 500

Met Ser Leu Thr Ser Ser Ser Ser Val Arg Val Glu Trp Ile Ala Ala
-25
-20
-15
-10

Val Thr Ile Ala Ala Gly Thr Ala Ala Ile Gly Tyr Leu Ala Tyr Lys
-5 1 5

Arg Phe Tyr Val Lys Asp His Arg Asn Lys Ala Met Ile Asn Leu His
10 15 20

Ile Gln Lys Asp Asn Pro Lys Ile Val His Ala Phe Asp Met Glu Asp 25 30 35

Leu Gly Asp Lys Ala Val Tyr Cys Arg Cys Trp Arg Ser Lys Lys Phe 40 45 50 55

Pro Phe Cys Asp Gly Ala His Thr Lys His Asn Glu Glu Thr Gly Asp
60 65 70

Asn Val Gly Pro Leu Ile Ile Lys Lys Lys Glu Thr
75 80

<210> 501

<211> 183

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -15..-1

<400> 501

Met Glu Ala Met Trp Leu Leu Cys Val Ala Leu Ala Val Leu Ala Trp
-15 -5 1

Gly Phe Leu Trp Val Trp Asp Ser Ser Glu Arg Met Lys Ser Arg Glu

<210> 502 <211> 98



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10
Gln Gly Arg Arg Leu Gly Ala Glu Ser Arg Thr Leu Leu Val Ile Ala
                            25
His Pro Asp Asp Glu Ala Met Phe Phe Ala Pro Thr Val Leu Gly Leu
Ala Arg Leu Arg His Trp Val Tyr Leu Leu Cys Phe Ser Ala Gly Asn
Tyr Tyr Asn Gln Gly Glu Thr Arg Lys Lys Glu Leu Leu Gln Ser Cys
                                    75
Asp Val Leu Gly Ile Pro Leu Ser Ser Val Met Ile Ile Asp Asn Arg
Asp Phe Pro Xaa Asp Pro Gly Met Gln Trp Asp Thr Xaa His Val Ala
        100
                            105
Xaa Val Leu Leu Gln His Ile Glu Val Asn Gly Ile Asn Leu Val Val
    115
                        120
                                            125
Thr Phe Asp Ala Gly Gly Xaa Ser Gly His Ser Asn His Ile Ala Leu
                    135
                                       140
Tyr Ala Ala Val Arg Lys Leu Glu Gly Gln Ile Cys Lys Pro Cys Gly
               150
                                   155
Thr Gly Gln Asp Phe Lys Glu
           165
```

<212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -15..-1 <400> 502 Met Glu Ala Met Trp Leu Leu Cys Val Ala Leu Ala Val Leu Ala Trp -10 Gly Phe Leu Trp Val Trp Asp Ser Ser Glu Arg Met Lys Ser Arg Glu Gln Gly Xaa Arg Leu Gly Ala Glu Ser Arg Thr Leu Leu Val Ile Ala His Pro Asp Asp Glu Ala Met Phe Phe Ala Pro Thr Val Leu Gly Leu 45 Ala Arg Leu Arg His Trp Val Tyr Leu Leu Cys Phe Ser Ala Val Phe 55 60 Arg Arg Glu Leu Ser Glu Tyr Thr Glu Xaa Leu Thr Ser Glu Pro Leu Xaa Ala

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<210> 503
<211> 183
<212> PRT
<213> Homo sapiens

<220>
<221> SIGNAL
<222> -57..-1

<400> 503
Met Asp Val Thr Gly Asp Glu Glu Glu Glu Ile Lys Gln Glu Ile Asn
-55
-50
-45
```



Met Leu Lys Lys Tyr Ser His His Arg Asn Ile Ala Thr Tyr Tyr Gly -35 -30 Ala Phe Ile Lys Lys Asn Pro Pro Gly Met Asp Asp Gln Leu Trp Leu -20 -15 Val Met Glu Phe Cys Gly Ala Gly Ser Val Thr Asp Leu Ile Lys Asn - 5 Thr Lys Gly Asn Thr Leu Lys Glu Glu Trp Ile Ala Tyr Ile Cys Xaa 10 15 Glu Ile Leu Arg Gly Leu Xaa His Leu His Gln His Lys Val Ile His Arg Xaa Ile Lys Gly Gln Asn Val Leu Leu Thr Glu Asn Ala Glu Val 50 Lys Leu Val Asp Phe Gly Xaa Xaa Ala Gln Leu Asp Arg Thr Val Gly Arg Xaa Asn Thr Phe Ile Gly Thr Pro Tyr Trp Met Ala Pro Xaa Val 80 Ile Ala Cys Asp Glu Asn Pro Xaa Ala Thr Tyr Asp Phe Lys Xaa Asp 95 Leu Trp Ser Leu Gly Ile Thr Ala Ile Glu Met Ala Glu Gly Leu Pro 110 Leu Ser Val Thr Cys Thr Pro

<210> 504

<211> 140

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -14..-1

<400> 504

Met Phe Leu Thr Ala Leu Leu Trp Arg Gly Arg Ile Pro Gly Arg Gln
-10 -5 1

Trp Ile Gly Lys His Arg Arg Pro Arg Phe Val Ser Leu Arg Ala Lys
5 10 15

Gln Asn Met Ile Arg Arg Leu Glu Ile Glu Ala Glu Asn His Tyr Trp
20 25 30

Leu Ser Met Pro Tyr Met Thr Arg Glu Gln Glu Arg Gly His Ala Ala 35 40 45 50

Leu Arg Arg Arg Glu Ala Phe Glu Ala Ile Lys Ala Ala Ala Thr Ser
55 60 65

Lys Phe Pro Pro His Arg Phe Ile Ala Asp Gln Leu Asp His Leu Asn 70 75 80

Xaa His Gln Glu Met Val Leu Ile Leu Ser Arg His Pro Trp Ile Leu 85 90 95

Trp Ile Thr Glu Leu Thr Ile Phe Thr Trp Ser Gly Leu Lys Asn Cys
100 105 110

Ser Leu Cys Glu Asn Glu Leu Trp Thr Ser Leu Tyr

<210> 505

<211> 59

<212> PRT

<213> Homo sapiens

<220>

**60** 

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<221> SIGNAL <222> -14..-1
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<400> 505

Met Ala Ala Leu Val Thr Val Leu Phe Thr Gly Val Arg Arg Leu His

Cys Ser Ala Xaa Leu Gly Arg Ala Ala Ser Gly Xaa Tyr Ser Arg Asn
5 10 15

Trp Leu Pro Thr Pro Pro Ala Thr Gly Pro Leu Pro Ser Ser Gln Thr 20 25 30

Gly His Met Arg Met Ala Ala Leu Leu Pro Gln

35 40

<210> 506

<211> 101 <212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -36..-1

<400> 506

Met Gly Pro Tyr Asn Val Ala Val Pro Ser Asp Val Ser His Ala Arg
-35
-30
-25

Phe Tyr Phe Leu Phe His Arg Pro Leu Arg Leu Leu Asn Leu Leu Ile
-20
-15
-10
-5

-20 -15 -10 -5 Leu Ile Glu Gly Ser Val Val Phe Tyr Gln Leu Tyr Ser Leu Leu Arg

Ser Glu Lys Trp Asn His Thr Leu Ser Met Ala Leu Ile Leu Phe Cys
15 20 25

Asn Tyr Tyr Val Leu Phe Lys Leu Leu Arg Asp Arg Xaa Xaa Leu Gly 30 35 40

Arg Ala Tyr Ser Tyr Pro Leu Asn Ser Tyr Glu Leu Lys Ala Asn Xaa 45. 50 55 60

Ala Ala Ser Xaa Gln

65

<210> 507

<211> 341

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -55..-1

<400> 507

Ala Leu Cys Lys Arg Leu Leu Ala Glu Asp Asp Glu Leu His Leu Cys

Leu Ala Cys Arg Asn Met Ser Lys Ala Glu Ala Val Cys Ala Ala Leu
-20 -15 -10

Leu Ala Ser His Pro Thr Ala Glu Val Thr Ile Val Gln Val Asp Val

Ser Asm Leu Gln Ser Phe Phe Arg Ala Ser Lys Glu Leu Lys Gln Arg
10 15 20 25



Phe Gln Arg Leu Asp Cys Ile Tyr Leu Asn Ala Gly Ile Met Pro Asn 30 Pro Gln Leu Asn Ile Lys Ala Leu Phe Phe Gly Leu Phe Ser Arg Lys Val Ile His Met Phe Ser Thr Ala Glu Gly Leu Leu Thr Gln Gly Asp 65 Lys Ile Thr Ala Asp Gly Leu Gln Glu Val Phe Glu Thr Asn Val Phe . 85 Gly His Phe Ile Leu Ile Arg Glu Leu Glu Pro Leu Cys His Ser 90 95 100 Asp Asn Pro Ser Gln Leu Ile Trp Thr Ser Ser Arg Ser Ala Arg Lys 115 110 Ser Asn Phe Ser Leu Glu Asp Phe Gln His Ser Lys Gly Lys Glu Pro 125 130 Tyr Ser Ser Ser Lys Tyr Ala Thr Asp Leu Leu Ser Val Ala Leu Asn 145 Arg Asn Phe Asn Gln Gln Gly Leu Tyr Ser Asn Val Ala Cys Pro Gly 160 Thr Ala Leu Thr Asn Leu Thr Tyr Gly Ile Leu Pro Pro Phe Ile Trp 175 180 Thr Leu Leu Met Pro Ala Ile Leu Leu Leu Arg Phe Phe Ala Asn Ala 190 195 Phe Thr Leu Thr Pro Tyr Asn Gly Thr Glu Ala Leu Val Trp Leu Phe 210 215 His Gln Lys Pro Glu Ser Leu Asn Pro Leu Ile Lys Tyr Leu Ser Ala 220 225 230 Thr Thr Gly Phe Gly Arg Asn Tyr Ile Met Thr Gln Lys Met Asp Leu 240 Asp Glu Asp Thr Ala Glu Lys Phe Tyr Gln Lys Leu Leu Glu Leu Glu 255 260 Lys His Ile Arg Val Thr Ile Gln Lys Thr Asp Asn Gln Ala Arg Leu 270 275 Ser Gly Ser Cys Leu

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